Harris A.
09/478'977

FILE 'REGISTRY' ENTERED AT 12:18:42 ON 26 MAR 2003
E COLLAGEN/CN 5
L1 408 S COLLAGEN ?/CN

-key terms

FILE 'HCAPLUS' ENTERED AT 12:18:53 ON 26 MAR 2003
L1 408 SEA FILE=REGISTRY ABB=ON PLU=ON COLLAGEN ?/CN
L2 80701 SEA FILE=HCAPLUS ABB=ON PLU=ON L1 OR COLLAGEN
L3 35340 SEA FILE=HCAPLUS ABB=ON PLU=ON L2 AND (MOAB OR MAB OR ANTIBOD? OR HU177 OR HUIV26 OR XL313 OR HU 177 OR HUIV 26 OR XL 313 OR PEPTID## OR PROTEIN OR POLYPEPTID## OR POLYPROTEIN OR OLIGONUCLEOTIDE OR OLIGO NUCLEOTIDE OR CYCLOPEPTID##)

Typos. Re-searched See last pgs.

L7 6430 SEA FILE=HCAPLUS ABB=ON PLU=ON ANGIOGENESIS(S)INHIBIT?

L8 306 SEA FILE=HCAPLUS ABB=ON PLU=ON L3 AND L7
L9 4 SEA FILE=HCAPLUS ABB=ON PLU=ON L8 AND (TRIPLE OR THREE)(W)(HELIX OR HELICAL?)

L1 408 SEA FILE=REGISTRY ABB=ON PLU=ON COLLAGEN ?/CN
L2 80701 SEA FILE=HCAPLUS ABB=ON PLU=ON L1 OR COLLAGEN
L3 35340 SEA FILE=HCAPLUS ABB=ON PLU=ON L2 AND (MOAB OR MAB OR ANTIBOD? OR HU177 OR HUIV26 OR XL313 OR HU 177 OR HUIV 26 OR XL 313 OR PEPTID## OR PROTEIN OR POLYPEPTID## OR POLYPROTEIN OR OLIGONUCLEOTIDE OR OLIGO NUCLEOTIDE OR CYCLOPEPTID##)
L7 6430 SEA FILE=HCAPLUS ABB=ON PLU=ON ANGIOGENESIS(S)INHIBIT?

L8 306 SEA FILE=HCAPLUS ABB=ON PLU=ON L3 AND L7
L10 16 SEA FILE=HCAPLUS ABB=ON PLU=ON L8 AND ((CYTOTOXIC OR CYTOSTATIC OR CYTO(W)(TOXIC OR STATIC))(5A)AGENT OR CYTOTOXIN OR CYTO TOXIN)

L11 19 L9 OR L10

L11 ANSWER 1 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:118026 HCAPLUS
DOCUMENT NUMBER: 138:165525
TITLE: Crystal structure of NC1 domain hexamer of bovine type IV **collagen** and application to drug screening and drug design
INVENTOR(S): Sundaramoorthy, Muirathinam; Hudson, Billy
PATENT ASSIGNEE(S): University of Kansas Medical Center, USA
SOURCE: PCT Int. Appl., 168 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003012122	A2	20030213	WO 2002-US23763	20020726

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ,

NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2001-308523P P 20010727
US 2001-351289P P 20011029
US 2002-366854P P 20020322
US 2002-385362P P 20020603

OTHER SOURCE(S): MARPAT 138:165525

AB The present invention provides a crystd. NC1 domain hexamer of bovine type IV **collagen**, and methods for making the crystal, wherein the NC1 domain hexamer is cystallized such that the three dimensional structure of the cystallized NC1 domain hexamer can be detd. to a resoln. of at least 3 .ANG. or better. The present invention also provides a method for designing compds. to **inhibit angiogenesis**, tumor growth, tumor metastasis, endothelial cell adhesion and/or proliferation, and/or basal lamina assembly, comprising analyzing the three dimensional structure of a cystallized type IV **collagen** NC1 domain hexamer produced by the methods of the invention, and identifying and synthesizing compds. that target regions of the NC1 domain that have been identified by the anal. as being important for type IV **collagen** heterotrimer and hexamer assembly. The present invention also provides novel **polypeptides** designed by the rational drug design methods of the present invention, based on an anal. of the type IV **collagen** NC1 hexamer structure disclosed herein.

L11 ANSWER 2 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2003:23522 HCAPLUS
DOCUMENT NUMBER: 138:66715
TITLE: Methods and compositions using human uteroglobin for the treatment of fibrotic conditions and impaired lung function and to enhance lymphocyte production
INVENTOR(S): Pilon, Aprile L.; Welch, Richard W.; Farrow, Jeffrey; Melby, James; Wiese, Laura; Lohnas, Gerald; Miele, Lucio; Antico, Gianni
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 60 pp., Cont.-in-part of U.S. Ser. No. 549,926.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003008816	A1	20030109	US 2001-835784	20010413
US 6255281	B1	20010703	US 1997-864357	19970528
US 2002160948	A1	20021031	US 1998-120264	19980721
US 2002169108	A1	20021114	US 2001-45534	20011024

PRIORITY APPLN. INFO.: US 1997-864357 A2 19970528
US 1998-87210 A2 19980528

US 1998-120264 A2 19980721
US 2000-549926 A2 20000414
US 2001-835784 A2 20010413

AB The invention provides methods and compns. to treat fibrotic conditions, to increase lymphocyte prodn. in vivo, and to improve and/or normalize lung function, pulmonary compliance, blood oxygenation, and blood pH to inhibit inflammatory processes to stimulate or inhibit pro-inflammatory and immune cells, and to inhibit migration of vascular endothelial cells. The invention discloses the administration of human uteroglobin, native or recombinant, as a means of achieving these ends. Specifically, it has been found that uteroglobin inhibits cell adhesion to fibronectin, increases lymphocyte prodn. in vivo, and improves and/or normalizes lung function, pulmonary compliance, blood oxygenation, and blood pH, and inhibits inflammatory process. In addn. it has been found that uteroglobin can stimulate or inhibit pro-inflammatory and immune cells and inhibitor migration of vascular endothelial cells.

L11 ANSWER 3 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:487906 HCAPLUS
DOCUMENT NUMBER: 137:68163
TITLE: Delivery of therapeutic agents
INVENTOR(S): Sirhan, Motasim; Yan, John
PATENT ASSIGNEE(S): Avantec Vascular Corporation, USA
SOURCE: U.S. Pat. Appl. Publ., 49 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002082679	A1	20020627	US 2001-2595	20011101
US 2002114823	A1	20020822	US 2001-782927	20010213
US 6471980	B2	20021029		
US 2003017190	A1	20030123	US 2002-242334	20020911

PRIORITY APPLN. INFO.:
US 2000-258024P P 20001222
US 2001-782804 A 20010213
US 2001-782927 A 20010213
US 2001-783253 A 20010213
US 2001-783254 A 20010213
US 2001-308381P P 20010726

AB A device and a method using the device for reducing restenosis and hyperplasia after intravascular intervention are disclosed. The present invention also provides luminal prostheses which allow for controlled release of at least one therapeutic agent with increased efficacy to selected locations within a patient vasculature to reduce restenosis. An intraluminal prosthesis may comprise an expandable structure and a source adjacent the expandable structure for releasing the therapeutic capable agent into the body lumen to reduce smooth muscle cell proliferation. A therapeutic agent, mycophenolic acid, was prepd. by dissolving it in acetone at 15 mg/mL. The amt. of the drug agent varied in the range 0.1 .mu.g-2 mg, preferably, at 600 .mu.g. The drug soln. was then coated onto or over a stent by spraying them with an atomizer sprayer, while the stent was rotated. The stent was allowed to let dry. The stent was

then placed over the tri-fold balloon on a catheter and crimped thereon. After crimping, the drug remained intact and attached to the stent. Expansion of the stent against a simulated Tecoflex vessel showed no cracking of the drug.

L11 ANSWER 4 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:314781 HCAPLUS
DOCUMENT NUMBER: 136:335266
TITLE: CD36-oxidized **protein** binding inhibitors and CD36 function inhibitors, their biological activity, and their therapeutic and diagnostic uses
INVENTOR(S): Kehrel, Beate; Brodde, Martin
PATENT ASSIGNEE(S): Germany
SOURCE: PCT Int. Appl., 88 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: German
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002032445	A2	20020425	WO 2001-EP12129	20011019
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
DE 10051983	A1	20020613	DE 2000-10051983	20001020
AU 2002015032	A5	20020429	AU 2002-15032	20011019

PRIORITY APPLN. INFO.: DE 2000-10051983 A 20001020
DE 2001-10148624 A 20011002
WO 2001-EP12129 W 20011019

AB The invention discloses substances which inhibit the binding of oxidized **proteins** to CD36 or inhibit the functions of CD36 that are induced by the interaction of CD36 with oxidized **proteins**. The invention also relates to the use of these substances as medicaments for humans and animals.

L11 ANSWER 5 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2002:107392 HCAPLUS
DOCUMENT NUMBER: 136:166062
TITLE: Endothelial cell expression patterns
INVENTOR(S): St. Croix, Brad; Kinzler, Kenneth W.; Vogelstein, Bert
PATENT ASSIGNEE(S): The Johns Hopkins University, USA
SOURCE: PCT Int. Appl., 331 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002010217	A2	20020207	WO 2001-US24031	20010801
WO 2002010217	C2	20030206		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

US 2003017157	A1	20030123	US 2001-918715	20010801
PRIORITY APPLN. INFO.:			US 2000-222599P	P 20000802
			US 2000-224360P	P 20000811
			US 2001-282850P	P 20010411

AB To gain a better understanding of tumor angiogenesis, new techniques for isolating endothelial cells (ECs) and evaluating gene expression patterns were developed. When transcripts from ECs derived from normal and malignant colorectal tissues were compared with transcripts from non-endothelial cells, over 170 genes predominantly expressed in the endothelium were identified. Comparison between normal- and tumor-derived endothelium revealed 79 differentially expressed genes, including 46 that were specifically elevated in tumor-assocd. endothelium. Expts. with representative genes from this group demonstrated that most were similarly expressed in the endothelium of primary lung, breast, brain, and pancreatic cancers as well as in metastatic lesions of the liver. These results demonstrate that neoplastic and normal endothelium in humans are distinct at the mol. level, and have significant implications for the development of anti-angiogenic therapies in the future.

L11 ANSWER 6 OF 19 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	2001:829297 HCAPLUS
DOCUMENT NUMBER:	136:181163
TITLE:	NC1 Domain of Human Type VIII **Collagen** (.alpha. 1) Inhibits Bovine Aortic Endothelial Cell Proliferation and Causes Cell Apoptosis
AUTHOR(S):	Xu, Ren; Yao, Zhong-Yin; Xin, Li; Zhang, Qian; Li, Tsai-Ping; Gan, Ren-Bao
CORPORATE SOURCE:	Institute of Biochemistry and Cell Biology, Shanghai Institute of Biological Sciences, Chinese Academy of Sciences, Shanghai, 200031, Peop. Rep. China
SOURCE:	Biochemical and Biophysical Research Communications (2001), 289(1), 264-268 CODEN: BBRCA9; ISSN: 0006-291X
PUBLISHER:	Academic Press
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Endostatin, a natural **angiogenesis inhibitor**, had been identified for years. It opened a new approach for cancer therapy. Sequence anal. revealed that endostatin is the NC1 domain

(non-**triple-helical** domain) of **collagen** XVIII. In this report, the cDNA of NC1 domain of type VIII **collagen** (.alpha. 1) was cloned and expressed as sol. form in Escherichia coli. The recombinant **protein** was purified with Ni-NTA agarose column and named as vastatin. It inhibited the proliferation of bovine aortic endothelial (BAE) cell stimulated by basic fibroblast growth factor (bFGF) in a dose-dependent manner. The ED50 of vastatin was 0.6 .mu.g/mL, while the ED50 of endostatin was 0.5 .mu.g/mL. Treatment of BAE cell with vastatin caused G0-G1 arrest and cell apoptosis. It is interesting that sequence anal. showed that there was only about 12% amino acid sequence homol. between vastatin and endostatin. The structure-function relationship of these angiogenesis mols. remains to be elucidated. (c) 2001 Academic Press.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 7 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:747553 HCAPLUS
DOCUMENT NUMBER: 135:287532
TITLE: Compositions and methods for **inhibition** of cancer invasion and **angiogenesis**
INVENTOR(S): Chen, Wen-tien
PATENT ASSIGNEE(S): The Research Foundation of State University of New York, USA
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001074299	A2	20011011	WO 2001-US10735	20010330
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 2001056975	A5	20011015	AU 2001-56975	20010330

PRIORITY APPLN. INFO.:

US 2000-193987P	P	20000401
US 2000-541785	A	20000403
WO 2001-US10735	W	20010330

AB The invention provides **antibodies** that specifically bind a membrane protease complex, the complex consisting of two homodimers of seprase and dipeptidyl peptidase IV (DPPIV), obtained from mammalian, preferably human cell membranes. The **antibodies** specifically bind the DPPIV protease of the seprase-DPPIV complex. This membrane protease complex resides on cell surface invadopodia at the leading edge of angiogenic endothelia, migratory fibroblasts,

and invading cancer cells. The **antibodies** and immunoconjugates of the invention specifically bind the membrane protease complex at the cell surface invadopodia, yet fail to react with resting cells in adjacent human tissues and blood vessels. These **antibodies** and immunoconjugates block interaction of **collagen** matrix with the seprase-DPPIV complex in the invasive cells during angiogenesis and cancer spreading but not that with other endothelia or tumor cells. The invention further provides methods for identifying and of using DPPIV antagonists to **inhibit** capillary sprouting, **angiogenesis** and cancer invasion in tumor tissues and metastases. Also provided are therapeutic compns. comprising DPPIV antagonists.

L11 ANSWER 8 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:660699 HCAPLUS
DOCUMENT NUMBER: 135:342351
TITLE: Proteolytic exposure of a cryptic site within **collagen** type IV is required for angiogenesis and tumor growth in vivo
AUTHOR(S): Xu, Jingsong; Rodriguez, Dorothy; Petitclerc, Eric; Kim, Jenny J.; Hangai, Masanori; Yuen, S. Moon; Davis, George E.; Brooks, Peter C.
CORPORATE SOURCE: Departments of Radiation Oncology and Cell Biology, Kaplan Cancer Center, New York University School of Medicine, New York, NY, 10016, USA
SOURCE: Journal of Cell Biology (2001), 154(5), 1069-1079
CODEN: JCLBA3; ISSN: 0021-9525
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Evidence is provided that proteolytic cleavage of **collagen** type IV results in the exposure of a functionally important cryptic site hidden within its **triple helical** structure. Exposure of this cryptic site was assocd. with angiogenic, but not quiescent, blood vessels and was required for angiogenesis in vivo. Exposure of the **HUIV26** epitope was assocd. with a loss of .alpha.1.beta.1 integrin binding and the gain of .alpha.v.beta.3 binding. A monoclonal **antibody** (**HUIV26**) directed to this site disrupts integrin-dependent endothelial cell interactions and potently **inhibits angiogenesis** and tumor growth. Together, these studies suggest a novel mechanism by which proteolysis contributes to angiogenesis by exposing hidden regulatory elements within matrix-immobilized **collagen** type IV.
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 9 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:624458 HCAPLUS
DOCUMENT NUMBER: 135:301342
TITLE: New collagenous **proteins**: FACITs, transmembrane **collagens** and multiplexins
AUTHOR(S): Gogiel, Tomasz; Bankowski, Edward
CORPORATE SOURCE: Zakl. Biochem., Akad. Med., Bialystok, 15-230,

Pol.
SOURCE: Postepy Higieny i Medycyny Doswiadczalnej (2001), 55(1), 133-156
CODEN: PHMDAD; ISSN: 0032-5449
PUBLISHER: Wydawnictwo Continuo
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Polish

AB A review with refs. **Collagens** are the main components of the extracellular matrix and they constitute about 30% of total body **protein**. Each **collagen** mol. consists of three **polypeptide** chains that intertwine in one or more places into **triple helical** domains, a very rare structure in other **proteins**. Nineteen **collagen** types have been described to date and these forming banded fibrils are the most abundant. In the last decade new collagenous **proteins** were discovered that have been classified into three distinct groups: fibril-assocd. **collagens** with interrupted **triple helixes** (FACITs), transmembrane **collagens** and multiplexins. FACITs appear to connect **collagen** fibrils to other matrix components or cells. Transmembrane **collagens** have intracellular domains and they participate in cell adhesion and probably in signal transduction. Multiplexins are situated mainly in basement membranes and contain sequences, which demonstrate features of **angiogenesis inhibitors** reducing the growth of neoplasmatic tumors.

L11 ANSWER 10 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:666622 HCAPLUS
DOCUMENT NUMBER: 133:232823
TITLE: Compositions and methods of use of LDL-like receptor ligands for the treatment of cancer and angiogenic-based disease
INVENTOR(S): Papathanassiu, Adonia E.; Green, Shawn J.
PATENT ASSIGNEE(S): Entremed, Inc., USA
SOURCE: PCT Int. Appl., 37 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000054801	A1	20000921	WO 2000-US7154	20000317
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1161258	A1	20011212	EP 2000-925874	20000317
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002539174	T2	20021119	JP 2000-604873	20000317

PRIORITY APPLN. INFO.: US 1999-270982 A 19990317
WO 2000-US7154 W 20000317

AB Compns. and methods effective in **inhibiting** abnormal or undesirable cell proliferation, particularly endothelial cell proliferation and **angiogenesis** related to neovascularization and tumor growth are provided. The compns. comprise a naturally occurring or synthetic **protein**, **peptide**, or **protein** fragment capable of binding to low d. lipoprotein (or low d. lipoprotein-like) receptors. The compns. may be administered using a pharmaceutically acceptable carrier. The methods involve administering to a human or animal the compns. described herein in a dosage sufficient to inhibit cell proliferation, particularly endothelial cell proliferation. The methods are useful for treating diseases and processes, such as cancer, mediated by undesired and uncontrolled cell proliferation particularly by **inhibiting angiogenesis**. Administration of the compns. of the present invention to a human or animal having prevascularized metastasized tumors is useful for preventing the growth or expansion of such tumors.

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 11 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:636163 HCAPLUS
DOCUMENT NUMBER: 133:227868
TITLE: Supplemented and unsupplemented tissue sealants, method of their production and use
INVENTOR(S): Macphee, Martin James; Drohan, William Nash; Liau, Gene; Haudenschild, Christian
PATENT ASSIGNEE(S): The American National Red Cross, USA
SOURCE: U.S., 79 pp., Cont.-in-part of U.S. Ser. No. 351,006, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 7
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6117425	A	20000912	US 1995-474086	19950607
EP 1142581	A2	20011010	EP 2001-113651	19911127
EP 1142581	A3	20020911		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AU 9884192	A1	19981105	AU 1998-84192	19980911
AU 733471	B2	20010517		

PRIORITY APPLN. INFO.: US 1990-618419 B2 19901127
US 1991-798919 B2 19911127
US 1993-31164 B1 19930312
US 1994-328552 B2 19941025
US 1994-351006 B2 19941207
EP 1992-901268 A3 19911127
AU 1994-63648 A3 19940314

AB This invention provides supplemented tissue sealants, methods for their prodn. and use thereof. Disclosed are tissue sealants supplemented with at least one **cytotoxin** or cell proliferation inhibiting compn. The compn. may be further

supplemented with, for example, one or more **antibodies**, analgesics, anticoagulants, anti-inflammatory compds., antimicrobial compns., cytokines, drugs, growth factors, interferons, hormones, lipids, demineralized bone or bone morphogenetic **proteins**, cartilage inducing factors, **oligonucleotides** polymers, polysaccharides, **polypeptides**, protease inhibitors, vasoconstrictors or vasodilators, vitamins, minerals, stabilizers and the like. Heparin binding growth factor-1 (HBGF-1) was added at 10 .mu.g in a fibrinogen complex contg. heparin 10, thrombin 0.5 U/mL, and CaCl2 40 mM for testing the HBGF-1 diffusion from a fibrin glue clot.

REFERENCE COUNT: 61 THERE ARE 61 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 12 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:475678 HCAPLUS
DOCUMENT NUMBER: 133:99569
TITLE: Method and composition for **angiogenesis inhibition** and detection using antagonists binding to proteolyzed or denatured **collagen**
INVENTOR(S): Brooks, Peter; Petitclerc, Eric; Xu, Jingsong
PATENT ASSIGNEE(S): University of Southern California, USA
SOURCE: PCT Int. Appl., 92 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000040597	A1	20000713	WO 2000-US383	20000106
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2358517	AA	20000713	CA 2000-2358517	20000106
EP 1149111	A1	20011031	EP 2000-904246	20000106
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002539076	T2	20021119	JP 2000-592305	20000106

PRIORITY APPLN. INFO.:

US 1999-114877P	P	19990106
US 1999-114878P	P	19990106
US 1999-143534P	P	19990713
US 1999-152496P	P	19990902
WO 2000-US383	W	20000106

AB The invention describes methods for **inhibiting angiogenesis** in a tissue by administering an antagonist that specifically binds to a proteolyzed or denatured **collagen** but not to native **triple helical** forms of the **collagen**. Antagonists of the invention can target e.g.

denatured **collagens** type I, type II, type III, type IV, type V, and combinations thereof. Methods using such antagonists for therapeutic treatment of tumor growth, tumor metastasis or of restenosis also are described, as are methods to use such antagonists as diagnostic markers of angiogenesis in normal or diseased tissues both in vivo and ex vivo. Antagonists include monoclonal **antibodies** referred to as HUI77, **HUIV26**, and **XL313**.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 13 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:314832 HCAPLUS
DOCUMENT NUMBER: 132:330632
TITLE: **Protein** and cDNA sequences of endostatin, and therapeutic anti-angiogenic compositions derived therefrom
INVENTOR(S): O'Reilly, Michael S.; Folkman, M. Judah
PATENT ASSIGNEE(S): The Children's Medical Center Corporation, USA
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000026368	A2	20000511	WO 1999-US25605	19991101
WO 2000026368	A3	20000810		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6346510	B1	20020212	US 1999-315689	19990520
EP 1124952	A2	20010822	EP 1999-962673	19991101
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.:

US 1998-106343P	P	19981030
US 1999-315689	A	19990520
US 1995-5835P	P	19951023
US 1996-23070P	P	19960802
US 1996-26263P	P	19960917
US 1996-740168	A3	19961022
US 1998-154302	A2	19980916
WO 1999-US25605	W	19991101

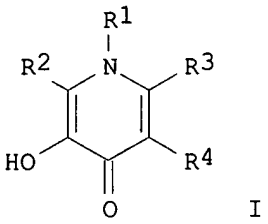
AB The invention provides **protein** and cDNA sequences of a novel **inhibitor** of **angiogenesis** (endostatin) which is useful for treating **angiogenesis**-related cancer and/or related disorders. Endostatin has a mol. wt. of approx. 10 to 20 kDa, is capable of inhibiting endothelial cell proliferation in cultured endothelial cells, and can be further characterized by

its N-terminal amino acid sequence which has identity to a C-terminal fragment of the NC1 domain of **collagen** XVIII. Endostatin compns. capable of **inhibiting** endothelial cell proliferation, **inhibiting angiogenesis** and causing tumor regression are described. The invention further relates to diagnostic assays and kits for endostatin measurement, to histochem. kits for localization of endostatin, to mol. probes to monitor endostatin biosynthesis, to **antibodies** that are specific for the endostatin, to the development of **peptide** agonists and antagonists to the endostatin receptor, and to **cytotoxic agents** linked to endostatin **peptides**.

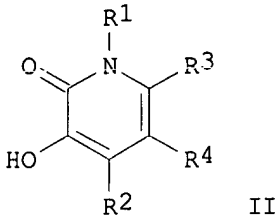
L11 ANSWER 14 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:219118 HCAPLUS
DOCUMENT NUMBER: 132:246381
TITLE: Method for the treatment of conditions mediated by **collagen** formation together with cell proliferation by application of hydroxypyridinone derivative inhibitors of **protein** hydroxylation
INVENTOR(S): Hanauske-Abel, Hartmut M.; McCaffrey, Timothy A.; Grady, Robert W.
PATENT ASSIGNEE(S): Cornell Research Foundation, Inc., USA
SOURCE: U.S., 29 pp., Cont.-in-part of U.S. 5,789,426. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6046219	A	20000404	US 1997-991913	19971216
US 5789426	A	19980804	US 1995-377137	19950120
CA 2210885	AA	19960725	CA 1996-2210885	19960117
US 5965585	A	19991012	US 1997-866998	19970530
US 5965586	A	19991012	US 1997-991758	19971216
US 6080766	A	20000627	US 1997-991124	19971216
WO 9930562	A1	19990624	WO 1998-US26646	19981215
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9917274	A1	19990705	AU 1999-17274	19981215
EP 1039804	A1	20001004	EP 1998-962117	19981215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1995-377137 A2 19950120
US 1997-991913 A 19971216
WO 1998-US26646 W 19981215
OTHER SOURCE(S): MARPAT 132:246381
GI



I



II

AB A method is provided for treating conditions mediated by **collagen** formation together with cell proliferation by administering to a patient or living system an effective amt. I or II (R1-R4 = H, alkyl, alkenyl, or alkoxy group contg. 1-8 C, aryl, aralkyl, or cycloalkyl group contg. 5-12 C, carboalkoxy or carbamyl contg. up to 8 C, **peptide** or peptidomimetic moiety contg. 10-30 C) or a deriv. thereof.

IT **9028-06-2**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hydroxypyridinone deriv. inhibitors of **protein** hydroxylation for treatment of conditions mediated by **collagen** formation together with cell proliferation)

REFERENCE COUNT: 42 THERE ARE 42 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 15 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:783929 HCAPLUS
DOCUMENT NUMBER: 132:18780
TITLE: Compositions comprising antimicrotubule agents for treating or preventing inflammatory diseases
INVENTOR(S): Hunter, William L.
PATENT ASSIGNEE(S): Angiotech Pharmaceuticals, Inc., Can.
SOURCE: PCT Int. Appl., 340 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 9962510	A2	19991209	WO 1999-CA464	19990601
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6495579	B1	20021217	US 1998-88546	19980601

PRIORITY APPLN. INFO.:

US 1998-88546	A	19980601
US 1996-32215P	P	19961202
US 1997-63087P	P	19971024
US 1997-980549	A2	19971201

AB Methods and compns. for treating or preventing inflammatory diseases, e.g. psoriasis or multiple sclerosis, are provided, comprising the step of delivering to the site of inflammation an antimicrotubule agent, or analog or deriv. thereof.

IT **9001-12-1**, Collagenase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(antimicrotubule agents for treating or preventing inflammatory diseases)

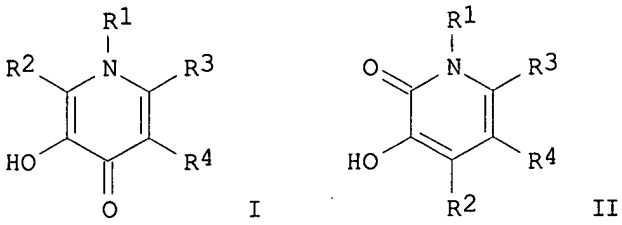
L11 ANSWER 16 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:401673 HCAPLUS
DOCUMENT NUMBER: 131:54041
TITLE: Method for treating fibroproliferative disorders by inhibitors of **protein** hydroxylation
INVENTOR(S): Hanauske-Abel, Hartmut M.; McCaffrey, Timothy A.; Grady, Robert W.
PATENT ASSIGNEE(S): Cornell Research Foundation, Inc., USA
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9930562	A1	19990624	WO 1998-US26646	19981215
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6046219	A	20000404	US 1997-991913	19971216
AU 9917274	A1	19990705	AU 1999-17274	19981215
EP 1039804	A1	20001004	EP 1998-962117	19981215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1997-991913 A 19971216
US 1995-377137 A2 19950120
WO 1998-US26646 W 19981215

OTHER SOURCE(S): MARPAT 131:54041

GI



I II

AB A method is provided for treating conditions mediated by **collagen** formation together with cell proliferation by administering to a patient or living system an effective amt. of a compd. I or II or a deriv. thereof (R1-R4 = H, alkyl, alkenyl, or alkoxy group contg. 1-8 carbon atoms, aryl, aralkyl, or cycloalkyl group contg. about 5-12 carbon atoms, or carboalkoxy or carbamyl group contg. up to 8 carbon atoms, or a **peptide** or peptidomimetic moiety contg. 10-30 carbon atoms).

IT **9028-06-2**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(hydroxypyridone deriv. **protein** hydroxylation inhibitors for fibroproliferative disorder treatment)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 17 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:277239 HCAPLUS
DOCUMENT NUMBER: 128:317264
TITLE: Method using 5-amino-1-[4-(4-chlorobenzoyl)-3,5-dichlorobenzyl]-1,2,3-triazole-4-carboxamide and related compounds for **inhibiting angiogenesis**
INVENTOR(S): Kohn, Elise C.; Liotta, Lance A.; Alessandro, Riccardo
PATENT ASSIGNEE(S): United States of America, USA
SOURCE: U.S., 14 pp., Cont.-in-part of U.S. Ser. No. 123,614, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

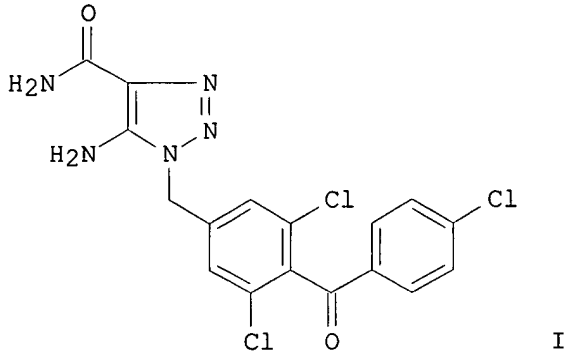
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5744492	A	19980428	US 1994-209651	19940310
WO 9508327	A1	19950330	WO 1994-US10550	19940916

W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES,

FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN
RW: KE, MW, SD, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

AU 9478754	A1	19950410	AU 1994-78754 19940916
PRIORITY APPLN. INFO.:			US 1993-123614 19930917
			US 1994-209651 19940310
			WO 1994-US10550 19940916

OTHER SOURCE(S): MARPAT 128:317264
GI



I

AB Angiogenesis is a composite of regulated proliferation and regulated invasion occurring in a variety of normal and pathol. conditions. The title compd. (I), and related analogs, are useful for **inhibiting angiogenesis** in a host and offer a novel approach to the treatment of cancer, diabetic retinopathy, hemangiomata, vasculidities and other diseases assocd. with **angiogenesis**.

L11 ANSWER 18 OF 19 HCAPLUS COPYRIGHT 2003 ACS

ACCESSION NUMBER:	1998:105199 HCAPLUS
DOCUMENT NUMBER:	128:213705
TITLE:	Antiangiogenic agent (TNP-470) inhibition of ectopic bone formation induced by bone morphogenetic **protein**-2
AUTHOR(S):	Mori, S.; Yoshikawa, H.; Hashimoto, J.; Ueda, T.; Funai, H.; Kato, M.; Takaoka, K.
CORPORATE SOURCE:	Department of Orthopaedic Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, 537, Japan
SOURCE:	Bone (New York) (1998), 22(2), 99-105 CODEN: BONEDL; ISSN: 8756-3282
PUBLISHER:	Elsevier Science Inc.
DOCUMENT TYPE:	Journal
LANGUAGE:	English

AB Bone morphogenetic **protein** (BMP) is a potent inducer of ectopic bone formation, and TNP-470, a synthetic analog of

fumagillin, is an antiangiogenic agent that strongly inhibits neovascular formation in vivo. The authors investigated the effects of TNP-470 on BMP-induced ectopic bone formation to clarify the role of angiogenesis in bone formation. **Collagen** pellets contg. recombinant human BMP-2 (rhBMP-2) were implanted beneath the fasciae of dorsal muscles in mice. By daily s.c. administration of TNP-470, ectopic new bone formation was inhibited in a dose-dependent manner. Histol. examn. revealed that TNP-470 prevented proliferation of mesenchymal cells and chondrogenesis at the initial step of endochondral bone formation. Immunohistochem. staining with a specific **antibody** against bone morphogenetic **protein** type IA receptor showed that TNP-470 reduced the no. of receptor-pos. cells surrounding the BMP pellets. The inhibitory effect of TNP-470 on bone formation continued during the period of its administration, and discontinuation of treatment was followed by the resumption of the whole process of endochondral bone formation. This study showed that TNP-470 reversibly **inhibits** the biol. activity of rhBMP-2 in the early stage of bone induction, suggesting that **angiogenesis** may play an essential role in the recruitment of BMP-receptor-pos. cells that can respond to rhBMP-2 and differentiate into chondrocytes and/or osteoblasts.

L11 ANSWER 19 OF 19 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1998:37377 HCAPLUS
DOCUMENT NUMBER: 128:176240
TITLE: Isolation and characterization of the circulating form of human endostatin
AUTHOR(S): Standker, Ludger; Schrader, Michael; Kanse, Sandip M.; Jurgens, Michael; Forssmann, Wolf-Georg; Preissner, Klaus T.
CORPORATE SOURCE: Lower Saxony Institute for Peptide Research (IPF), Hannover, D-30625, Germany
SOURCE: FEBS Letters (1997), 420(2,3), 129-133
CODEN: FEBLAL; ISSN: 0014-5793
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Recently, fragments of extracellular **proteins**, including endostatin, were defined as a novel group of **angiogenesis inhibitors**. In this study, human plasma equiv. hemofiltrate was used as a source for the purifn. of high mol. wt. **peptides** (10-20 kDa), and the isolation and identification of circulating human endostatin are described. The purifn. of this C-terminal fragment of **collagen** .alpha.1(XVIII) was guided by MALDI-MS and the exact mol. mass detd. by ESI-MS was found to be 18494 Da. N-terminal sequencing revealed the identity of this putative **angiogenesis inhibitor** and its close relation to mouse endostatin. The cysteine residues 1-3 and 2-4 in the mol. are linked by disulfide bridges. In vitro biol. characterization of the native **protein** demonstrated no anti-proliferative activity on different endothelial cell types. These data indicate that human endostatin, which is a putative **angiogenesis inhibitor**, is present in the circulation.
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 12:31:07 ON 26 MAR 2003)

L12 19 S L9
L13 10 S L10
L14 26 S L12 OR L13
L15 13 DUP REM L14 (13 DUPLICATES REMOVED)

L15 ANSWER 1 OF 13 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2001-656962 [75] WPIDS
DOC. NO. CPI: C2001-193302
TITLE: New **antibodies** useful for treating growth and proliferative disorders involving angiogenesis such as cancer and tumor, comprise **antibodies** specific to the epitope of dipeptidyl peptidase IV.
DERWENT CLASS: B04 D16
INVENTOR(S): CHEN, W
PATENT ASSIGNEE(S): (UYNY) UNIV NEW YORK STATE RES FOUND; (CHEN-I) CHEN W
COUNTRY COUNT: 95
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001074299	A2	20011011	(200175)*	EN	77

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

AU 2001056975	A	20011015	(200209)	
US 2002132979	A1	20020919	(200264)	

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001074299	A2	WO 2001-US10735	20010330
AU 2001056975	A	AU 2001-56975	20010330
US 2002132979	A1 Provisional	US 2000-193987P	20000401
	CIP of	US 2000-541785	20000403
		US 2001-823277	20010330.

FILING DETAILS:

PATENT NO	KIND	PATENT NO
AU 2001056975	A Based on	WO 200174299

PRIORITY APPLN. INFO: US 2000-541785 20000403; US 2000-193987P 20000401; US 2001-823277 20010330
AN 2001-656962 [75] WPIDS
AB WO 200174299 A UPAB: 20021031
NOVELTY - A monospecific **antibody** (I) which specifically binds an epitope of a mammalian serine integral membrane protease,

dipeptidyl peptidase IV (DPPIV) (also known as CD26), is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a bispecific **antibody** (II) with binding specificity for a first epitope and a second epitope, where the first epitope is the epitope bound by (I);

(2) an immunoconjugate (III) comprising (I) or (II) joined to a therapeutic agent;

(3) a pharmaceutical composition (IV) for **inhibiting angiogenesis** comprising (I), (II) or (III) and a pharmaceutically acceptable carrier;

(4) a continuous cell line (V) producing (I); and

(5) stimulating (M1) angiogenesis in a mammal suffering from disease or disorder that may be remedied by an increased blood supply, comprising administering DPPIV modulator, where the blood supply to the affected tissue is increased.

ACTIVITY - Antitumor; Cytostatic; Cardiant; Antidiabetic; Antiulcer; Ophthalmological; Vulnerary. Human breast carcinoma cell line MDA-MB-436 (seprase+DPPIV) and human malignant melanoma cell line LOX (seprase+DPPIV-) were transformed with a retrovirus vector for lacZ tag as described Kern et al., 1994 and 0.5 multiply 106 of these cells were subcutaneously injected into 6-8 week-old female athymic mice. **Antibodies** or inhibitors were subcutaneously co-inoculated orthotopically with human cancer cells (seprase+DPPIV+ and seprase+DPPIV-), followed by intravenous injection into the tail vein with 250 mu g of the **mAb** E19, E26 or E3 (anti-DPPIV). Mice were maintained for 2-3 months or until primary tumor reaching 2 cm in diameter, after which the primary tumor and selected organs (lung and liver) were assayed for beta -galactosidase activity. The morphological examination of the established tumors and lung metastases revealed that invasion and metastasis of human cancer cells into mouse tissue had occurred.

MECHANISM OF ACTION - **Angiogenesis inhibitor** ; DPPIV modulator (stimulator) (claimed); seprase-DPPIV antagonist. No biological data was provided.

USE - (I), (II), (III) or (IV) is useful for treating a patient suffering from a growth or proliferative disorder involving **angiogenesis**, preferably in combination with chemotherapy regimen (claimed). (I) is useful for **inhibiting** (M2) cancer invasion and **angiogenesis** in a solid tumor which is metastasized in a patient preferably human where cells of normal tissues do not express levels of DPPIV-seprase complex detected by immunohistochemistry. The method comprises administering a composition comprising (I) to the patient where DPPIV-seprase complex expressed on surface of vascular endothelial cells and invading cancer cells involved in the cancer invasion and **angiogenesis**, is contacted by (I) which **inhibits** binding of **collagen** to the complex, resulting in **inhibition** of cancer invasion and limiting the blood supply to the tissue of the solid tumor. The method is conducted preferably in conjugation with chemotherapy or with administration of a **cytotoxin** conjugate (claimed). (M1) is useful for stimulating **angiogenesis** in a mammal suffering from disease or disorder such as cardiovascular disease, a diabetic ulcer, retinopathy or a non-healing wound, that may be remedied by an increased blood supply (claimed).

Dwg.0/9

L15 ANSWER 2 OF 13 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2001-256352 [26] WPIDS
CROSS REFERENCE: 1992-216795 [26]; 1994-302683 [37]; 1996-300272 [30]; 1997-087008 [08]; 2000-618127 [54]
DOC. NO. NON-CPI: N2001-182713
DOC. NO. CPI: C2001-077142
TITLE: Localized sustained delivery of supplements to promote (re)generation of bone and/or cartilage by preparing and applying biocompatible supplemented tissue sealant composition.
DERWENT CLASS: B04 B07 D22 P32
INVENTOR(S): DROHAN, W N; HAUDENSCHILD, C; LASA, C I; LIAU, G; MACPHEE, M J
PATENT ASSIGNEE(S): (AMNA-N) AMERICAN NAT RED CROSS
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
US 6197325	B1	20010306	(200126)*		79

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
US 6197325	B1	CIP of	US 1990-618419	19901127
		CIP of	US 1991-798919	19911127
		Cont of	US 1993-31164	19930312
		CIP of	US 1994-328552	19941025
		CIP of	US 1994-351006	19941207
			US 1995-474084	19950607

PRIORITY APPLN. INFO: US 1995-474084 19950607; US 1990-618419 19901127; US 1991-798919 19911127; US 1993-31164 19930312; US 1994-328552 19941025; US 1994-351006 19941207

AN 2001-256352 [26] WPIDS
CR 1992-216795 [26]; 1994-302683 [37]; 1996-300272 [30]; 1997-087008 [08]; 2000-618127 [54]
AB US 6197325 B UPAB: 20011121
NOVELTY - Localized sustained delivery of supplements to promote (re)generation of bone and/or cartilage for longer than according to simple diffusion kinetics comprises preparing a biocompatible supplemented tissue sealant composition and applying it to a site needing newly formed bone and/or cartilage under conditions suitable for inducing formation of a fibrin matrix.

DETAILED DESCRIPTION - Localized sustained delivery of supplements to promote generation or regeneration of bone and/or cartilage comprises:

(a) preparing a biocompatible supplemented tissue sealant composition comprising supplement(s) comprising **cytotoxin** or cell proliferation inhibiting compound, osteogenic compound, osteoconductive compound, cartilage inducing compound, **oligonucleotide**, polynucleotide, a compound that inhibits the differentiation cells involved in the formation or metabolism of bone, a compound that induces the differentiation of cells involved in the formation or metabolism of bone and/or a compound that

prevents resorption of bone in amount(s) that promote generation or regeneration of bone and/or cartilage and fibrinogen or its derivatives or metabolites comprising fibrin I and II in amounts that form a fibrin matrix in the presence of thrombin and calcium (II) ions and water and

(b) applying the composition to a site needing newly formed bone and/or cartilage under conditions suitable for inducing formation of a fibrin matrix, which provides a scaffold that determines the shape and location of the newly formed bone and/or cartilage. The amount of supplement is greater than the amount that is soluble in the fibrin matrix and the sustained delivery is for a period greater than the period obtained according to simple diffusion kinetics.

ACTIVITY - Osteopathic; vulnerary.

MECHANISM OF ACTION - Cell proliferation inhibitor; cartilage inducer; fibroblast growth factor; platelet-derived growth factor; insulin-binding growth factor; epidermal growth factor; transforming growth factor; bone growth factor; bone morphogenetic growth factor; **collagen** growth factor; heparin-binding growth factor; cartilage-inducing factor; osteoid-inducing factor.

USE - Used for localized sustained delivery of supplements to promote (re)generation of bone and/or cartilage (claimed), promote wound healing, promote the endothelialization of vascular prostheses, promote the proliferation and/or differentiation of animal cells and promote the localized delivery of drug(s) or growth factors. The method can be used to provide a simple-to-use, fast-acting, field-ready fibrin bandage for applying a tissue sealing composition to wounded tissue.

ADVANTAGE - The method provides sustained delivery for periods longer than those obtained according to simple diffusion kinetics. The sealants used do not **inhibit** full thickness skin wound healing and have many of the characteristics of an ideal biodegradable carrier, so that they can be formulated to contain only human **proteins** thus eliminating or minimizing immunogenicity probes and foreign body reactions, their administration is versatile, and their removal from host tissues is not required because they are degraded by the host's own natural fibrinolytic system. The method allows effective delivery of growth factors and/or drugs for prolonged periods of time to internal or external wounds, allowing prolonged contact between the growth factor and its receptors, and the production of strong biological effects. Animal cells can migrate into and through, and grow in the tissue sealants to aid engraftment of the cells to neighboring tissues and prostheses. Because of the initial liquid nature, the sealants can cover surfaces more thoroughly and completely than many prior art delivery systems, an advantage for coating biomaterials and in the endothelialization of vascular prostheses. The sealants can be molded and thus can be made into desired shapes. Antibiotic supplements increase the longevity and long-term stability of fibrin glues, allowing localized, long-term delivery of drug and/or growth factors, even after the stabilizing drug has substantially left the sealant. The method allows site-directed **angiogenesis** to incur in vivo promoted by the sealant. The method uses sealant components that can be formulated into simple-to-use, fast-acting field dressings, making it possible to control bleeding from hemorrhaging trauma wounds increase the number of lives saved and providing easy-to-use first-aid treatments that will, in emergency or disaster situations, allowing untrained individuals to treat

traumatic injuries to control hemorrhage until medical assistance is available.
Dwg.0/42

L15 ANSWER 3 OF 13 MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001227983 MEDLINE
DOCUMENT NUMBER: 21157402 PubMed ID: 11257123
TITLE: Oligomerization-dependent regulation of motility and morphogenesis by the **collagen** XVIII NC1/endostatin domain.
AUTHOR: Kuo C J; LaMontagne K R Jr; Garcia-Cardena G; Ackley B D; Kalman D; Park S; Christofferson R; Kamihara J; Ding Y H; Lo K M; Gillies S; Folkman J; Mulligan R C; Javaherian K
CORPORATE SOURCE: Department of Surgery, Children's Hospital, Harvard Medical School, Boston. Massachusetts 02115, USA.. cjkuo@stanford.edu
CONTRACT NUMBER: R35CA44338 (NCI)
SOURCE: JOURNAL OF CELL BIOLOGY, (2001 Mar 19) 152 (6) 1233-46.
Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200104
ENTRY DATE: Entered STN: 20010502
Last Updated on STN: 20010502
Entered Medline: 20010426

AB **Collagen** XVIII (c18) is a **triple helical** endothelial/epithelial basement membrane **protein** whose noncollagenous (NC)1 region trimerizes a COOH-terminal endostatin (ES) domain conserved in vertebrates, Caenorhabditis elegans and Drosophila. Here, the c18 NC1 domain functioned as a motility-inducing factor regulating the extracellular matrix (ECM)-dependent morphogenesis of endothelial and other cell types. This motogenic activity required ES domain oligomerization, was dependent on rac, cdc42, and mitogen-activated **protein** kinase, and exhibited functional distinction from the archetypal motogenic scatter factors hepatocyte growth factor and macrophage stimulatory **protein**. The motility-inducing and mitogen-activated **protein** kinase-stimulating activities of c18 NC1 were blocked by its physiologic cleavage product ES monomer, consistent with a proteolysis-dependent negative feedback mechanism. These data indicate that the **collagen** XVIII NC1 region encodes a motogen strictly requiring ES domain oligomerization and suggest a previously unsuspected mechanism for ECM regulation of motility and morphogenesis.

L15 ANSWER 4 OF 13 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001493142 MEDLINE
DOCUMENT NUMBER: 21426955 PubMed ID: 11535623
TITLE: Proteolytic exposure of a cryptic site within **collagen** type IV is required for angiogenesis and tumor growth in vivo.
COMMENT: Erratum in: J Cell Biol 2001 Nov 26;155(5):859
Erratum in: Yuen SM [corrected to Moon YS]
AUTHOR: Xu J; Rodriguez D; Petitclerc E; Kim J J; Hangai M;

Moon Y S; Davis G E; Brooks P C; Yuen S M
CORPORATE SOURCE: Department of Radiation Oncology, Kaplan Cancer Center, New York University School of Medicine, New York, NY 10016, USA.
CONTRACT NUMBER: CA086140 (NCI)
CA74132 (NCI)
HL59971 (NHLBI)
SOURCE: JOURNAL OF CELL BIOLOGY, (2001 Sep 3) 154 (5) 1069-79.
Journal code: 0375356. ISSN: 0021-9525.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200110
ENTRY DATE: Entered STN: 20010906
Last Updated on STN: 20020125
Entered Medline: 20011004

AB Evidence is provided that proteolytic cleavage of **collagen** type IV results in the exposure of a functionally important cryptic site hidden within its **triple helical** structure. Exposure of this cryptic site was associated with angiogenic, but not quiescent, blood vessels and was required for **angiogenesis** in vivo. Exposure of the **HUIV26** epitope was associated with a loss of alphalbeta1 integrin binding and the gain of alphavbeta3 binding. A monoclonal **antibody** (**HUIV26**) directed to this site disrupts integrin-dependent endothelial cell interactions and potently **inhibits** **angiogenesis** and tumor growth. Together, these studies suggest a novel mechanism by which proteolysis contributes to **angiogenesis** by exposing hidden regulatory elements within matrix-immobilized **collagen** type IV.

L15 ANSWER 5 OF 13 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2001688803 MEDLINE
DOCUMENT NUMBER: 21565917 PubMed ID: 11708810
TITLE: NC1 domain of human type VIII **collagen** (alpha 1) inhibits bovine aortic endothelial cell proliferation and causes cell apoptosis.
AUTHOR: Xu R; Yao Z Y; Xin L; Zhang Q; Li T P; Gan R B
CORPORATE SOURCE: Institute of Biochemistry and Cell Biology, Shanghai Institute of Biological Sciences, Chinese Academy of Sciences, 320 Yue Yang Road, Shanghai 200031, People's Republic of China.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (2001 Nov 23) 289 (1) 264-8.
Journal code: 0372516. ISSN: 0006-291X.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200112
ENTRY DATE: Entered STN: 20011210
Last Updated on STN: 20020123
Entered Medline: 20011227

AB Endostatin, a natural **angiogenesis inhibitor**, had been identified for years. It opened a new approach for cancer therapy. Sequence analysis revealed that endostatin is the NC1

domain (non-**triple-helical** domain) of **collagen** XVIII. In this report, the cDNA of NC1 domain of type VIII **collagen** (alpha 1) was cloned and expressed as soluble form in Escherichia coli. The recombinant **protein** was purified with Ni-NTA agarose column and named as vastatin. It **inhibited** the proliferation of bovine aortic endothelial (BAE) cell stimulated by basic fibroblast growth factor (bFGF) in a dose-dependent manner. The ED(50) of vastatin was 0.6 microg/ml, while the ED(50) of endostatin was 0.5 microg/ml. Treatment of BAE cell with vastatin caused G(0)-G(1) arrest and cell apoptosis. It is interesting that sequence analysis showed that there was only about 12% amino acid sequence homology between vastatin and endostatin. The structure-function relationship of these **angiogenesis** molecules remains to be elucidated.
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L15 ANSWER 6 OF 13 MEDLINE
ACCESSION NUMBER: 2001263177 MEDLINE
DOCUMENT NUMBER: 21254963 PubMed ID: 11355528
TITLE: [New collagenous **proteins**: FACIT **collagens**, transmembrane **collagens** and multiplexins].
Nowe bialka kolagenowe: kolageny FACIT, transblonowe i multipleksyny.
AUTHOR: Gogiel T; Bankowski E
CORPORATE SOURCE: Zaklad Biochemii Akademii Medycznej w Bialymstoku.
SOURCE: POSTEPY HIGIENY I MEDYCYNY DOSWIADCZALNEJ, (2001) 55 (1) 133-56. Ref: 82
Journal code: 0421052. ISSN: 0032-5449.
PUB. COUNTRY: Poland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: Polish
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200107
ENTRY DATE: Entered STN: 20010709
Last Updated on STN: 20010709
Entered Medline: 20010705

AB **Collagens** are the main components of the extracellular matrix and they constitute about 30% of total body **protein** . Each **collagen** molecule consists of three **polypeptide** chains that intertwine in one or more places into **triple helical** domains, a very rare structure in other **proteins**. Nineteen **collagen** types have been described to date and these forming banded fibrils are the most abundant. In the last decade new collagenous **proteins** were discovered that have been classified into three distinct groups: fibril-associated **collagens** with interrupted **triple helices** (FACITs), transmembrane **collagens** and multiplexins. FACITs appear to connect **collagen** fibrils to other matrix components or cells. Transmembrane **collagens** have intracellular domains and they participate in cell adhesion and probably in signal transduction. Multiplexins are situated mainly in basement membranes and contain sequences, which demonstrate features of **angiogenesis inhibitors** reducing the growth of neoplasmatic tumours.

L15 ANSWER 7 OF 13 WPIDS (C) 2003 THOMSON DERWENT
ACCESSION NUMBER: 2000-572263 [53] WPIDS
CROSS REFERENCE: 2003-165809 [16]
DOC. NO. NON-CPI: N2000-423321
DOC. NO. CPI: C2000-170670
TITLE: **Antibody** or its antigen-binding fragment which binds to the mammalian CC chemokine receptor GPR-9-6, useful for treating inflammatory diseases, cancer or inhibiting GPR-9-6-mediated homing of leukocytes to mucosal tissue.
DERWENT CLASS: B04 C03 D16 S03
INVENTOR(S): ANDREW, D P; PONATH, P D; ZABEL, B A
PATENT ASSIGNEE(S): (MILL-N) MILLENNIUM PHARM INC; (LEUK-N) LEUKOSITE INC
COUNTRY COUNT: 92
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000053635	A1	20000914	(200053)*	EN	114
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW					
AU 2000035226	A	20000928	(200067)		
EP 1157043	A1	20011128	(200201)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
US 6329159	B1	20011211	(200204)		
US 2002119504	A1	20020829	(200259)		
MX 2001007200	A1	20011201	(200282)		
JP 2002542157	W	20021210	(200301)		141
US 2003022238	A1	20030130	(200311)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2000053635	A1		WO 2000-US6240	20000310
AU 2000035226	A		AU 2000-35226	20000310
EP 1157043	A1		EP 2000-913864	20000310
			WO 2000-US6240	20000310
US 6329159	B1		US 1999-266464	19990311
US 2002119504	A1	Div ex	US 1999-266464	19990311
			US 2001-952385	20010913
MX 2001007200	A1		MX 2001-7200	20010716
JP 2002542157	W		JP 2000-604070	20000310
			WO 2000-US6240	20000310
US 2003022238	A1	Div ex	US 1999-266464	19990311
			US 2001-966755	20010928

FILING DETAILS:

PATENT NO	KIND	PATENT NO

AU 2000035226 A Based on WO 200053635
EP 1157043 A1 Based on WO 200053635
JP 2002542157 W Based on WO 200053635
US 2003022238 A1 Div ex US 6329159

PRIORITY APPLN. INFO: US 1999-266464 19990311; US 2001-952385 20010913; US 2001-966755 20010928
AN 2000-572263 [53] WPIDS
CR 2003-165809 [16]
AB WO 200053635 A UPAB: 20030307
NOVELTY - An **antibody** (AB1) or its antigen-binding fragment which binds to the mammalian CC chemokine receptor GPR-9-6, and blocks the binding of a ligand (e..g TECK) to the receptor, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) an **antibody** produced by murine hybridoma 3C3 or its antigen-binding fragment;

(2) an isolated cell which produces AB1 or its antigen-binding fragment;

(3) murine hybridoma 3C3;

(4) a method (M1) of detecting a mammalian GPR-9-6 or its portion in a biological sample, comprising:

(a) contacting a biological sample with an **antibody** or its antigen-binding fragment which binds to a mammalian GPR-9-6 or a portion of the receptor, and inhibits binding of a ligand to the receptor, under conditions appropriate for binding of the **antibody** to the receptor; and

(b) detecting binding of the **antibody** or its antigen-binding fragment

(5) a method (M2) of detecting and identifying an agent which binds to a mammalian GPR-9-6 or its ligand binding variant, comprising combining:

(a) a reference agent;

(b) a test agent; and

(c) a composition comprising a functional mammalian GPR-9-6 or its ligand binding variant under conditions suitable for binding of the reference agent to the GPR-9-6 or its ligand-binding variant; and

(d) detecting or measuring the formation of a complex between the reference agent and the GPR-9-6 or its ligand binding variant; where a decrease in the formation of the complex relative to a suitable control indicates that the test agent binds to the GPR-9-6 or to its ligand binding variant

(6) a method (M3) of detecting or identifying an inhibitor of a mammalian GPR-9-6 receptor comprising:

(a) combining an agent to be tested, a ligand or promoter of the GPR-9-6 and a cell expressing the GPR-9-6 under conditions suitable for detecting a ligand- or promoter-induced response; and

(b) determining the ability of the test compound to inhibit the response;

(7) a method (M4) of treating an inflammatory disease, cancer or inhibiting GPR-9-6-mediated homing of leukocytes to mucosal tissue, comprising administering an effective amount of an antagonist of a mammalian GPR-9-6;

(8) a method (M5) of modulating a GPR-9-6 function, comprising contacting a cell that expresses GPR-9-6 with an agent which binds to it, therefore modulating the function of GPR-9-6;

(9) a test kit for carrying out the method of M1, comprising at least one **antibody** or its antigen-binding fragment which binds to mammalian GPR-9-6 and one or more ancillary reagents suitable for detecting the presence of a complex between the **antibody** and the receptor;

(10) an **antibody** (AB2) or its antigen-binding fragment, which binds to a mammalian, preferably human, TECK and inhibits the binding of the TECK to a GPR-9-6 receptor;

(11) an **antibody** or its antigen-binding fragment produced by murine hybridoma GPR96-1, 11.3.1 or 16.3.1;

(12) murine hybridomas GPR96-1, 16.3.1 and 11.3.1;

(13) an isolated cell which produces AB or its antigen-binding fragment;

(14) a method (M6) of detecting a mammalian TECK or its portion in a biological sample, comprising:

(a) contacting a biological sample with an **antibody** or its antigen-binding fragment which binds to a mammalian TECK or its portion, and inhibits binding of a TECK to its receptor; and

(b) detecting binding of the **antibody** or its antigen-binding fragment;

(15) a test kit for carrying out the method of M6, comprising at least one **antibody** or its antigen-binding fragment which binds to mammalian TECK and one or more ancillary reagents suitable for detecting the presence of a complex between the **antibody** and TECK;

(16) a method (M7) of treating a subject having cancer, comprising administering to an effective amount of an immunoconjugate or antigen-binding fusion **protein**, where the immunoconjugate or antigen-binding fusion **protein** comprises at least an antigen-binding portion (ABP) of an **antibody** which binds GPR-9-6 and which is directly or indirectly bonded to an additional therapeutic agent;

(17) an immunoconjugate comprising an ABP of an **antibody** which binds GPR-9-6 and which is directly or indirectly bonded to an additional therapeutic agent; and

(18) an antigen-binding fusion protein comprising an ABP of an antibody which binds GPR-9-6 and which is directly or indirectly bonded to an additional therapeutic agent, where the ABP and therapeutic agent are part of a contiguous polypeptide.

ACTIVITY - Antiinflammatory; cytostatic; Antiasthmatic; antiallergic; antidiabetic; neuroprotective; antiviral; antibacterial; antiangiogenic; antirheumatic; antiarthritic; antiarteriosclerotic.

No biological data given.

MECHANISM OF ACTION - Antagonist; The antibody binds to the GPR-9-6 receptor or to its ligand (e.g. TECK), therefore inhibiting the binding between the receptor and its ligand.

USE - The antibodies can be used to detect or measure expression of GPR-9-6 receptor. They can also be used to detect TECK. The antibodies are useful for treating an inflammatory disease, cancer and inhibiting GPR-9-6-mediated homing of leukocytes to mucosal tissue.

The cancer treated is acute or chronic leukemia (e.g., acute T-cell lymphoblastic leukemia, acute B-cell lymphoblastic leukemia, chronic T-cell lymphoblastic leukemia, chronic B-cell lymphoblastic leukemia), lymphoma (e.g., Hodgkin's disease, T cell lymphoma) or carcinoma (e.g., breast, melanoma, myeloma, or adenoma).

The inflammatory diseases treated are Crohn's disease, colitis,

inflammatory bowel disease (claimed), mastitis, vaginitis, cholangitis or pericholangitis, chronic bronchitis, asthma, graft versus host disease, hypersensitivity pneumonitis, collagen diseases, sarcoidosis, and other idiopathic conditions.

Other diseases that can be treated by the antibodies are autoimmune diseases (e.g. rheumatoid arthritis, multiple sclerosis), infectious diseases (e.g. bacterial and viral infections), atherosclerosis, restenosis, AIDS, pancreatitis, insulin-dependent diabetes mellitus, and diseases in which angiogenesis or neovascularization play a role.

Dwg.0/24

L15 ANSWER 8 OF 13 WPIDS (C) 2003 THOMSON DERWENT

ACCESSION NUMBER: 2000-465948 [40] WPIDS
DOC. NO. CPI: C2000-140343
TITLE: New antagonist that specifically binds to a denatured **collagen**, but binds to the native **triple helical** form of **collagen** with substantially reduced affinity, useful for **inhibiting angiogenesis**.
DERWENT CLASS: B04 C06 D16
INVENTOR(S): BROOKS, P; JINGSONG, X; PETITCLERC, E; XU, J
PATENT ASSIGNEE(S): (UYSC-N) UNIV SOUTHERN CALIFORNIA
COUNTRY COUNT: 90
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000040597	A1	20000713	(200040)*	EN	92
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW					
AU 2000026032	A	20000724	(200052)		
EP 1149111	A1	20011031	(200172)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
CN 1345331	A	20020417	(200248)		
JP 2002539076	W	20021119	(200281)		136

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000040597	A1	WO 2000-US383	20000106
AU 2000026032	A	AU 2000-26032	20000106
EP 1149111	A1	EP 2000-904246	20000106
		WO 2000-US383	20000106
CN 1345331	A	CN 2000-802601	20000106
JP 2002539076	W	JP 2000-592305	20000106
		WO 2000-US383	20000106

FILING DETAILS:

PATENT NO	KIND	PATENT NO

AU 2000026032 A Based on WO 200040597
EP 1149111 A1 Based on WO 200040597
JP 2002539076 W Based on WO 200040597

PRIORITY APPLN. INFO: US 1999-152496P 19990902; US 1999-114877P 19990106; US 1999-114878P 19990106; US 1999-143534P 19990713

AN 2000-465948 [40] WPIDS

AB WO 200040597 A UPAB: 20000823

NOVELTY - An antagonist (I) that specifically binds to a denatured **collagen**, but binds to the native **triple helical** form of **collagen** with substantially reduced affinity, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) detecting angiogenesis in a tissue by contacting (I) with the tissue;

(2) detecting tumors or tumor invasion in a tissue by administering (I);

(3) screening for denatured **collagen** antagonists comprising:

(a) providing a putative antagonist;

(b) measuring the putative antagonists first affinity for a denatured type I, II, III, IV or V **collagen**;

(c) measuring the putative antagonists second affinity for a native type I, II, III, IV or V **collagen**, where the native **collagen** selected is the same type as the denatured **collagen** selected; and

(d) selecting the putative antagonist as a denatured **collagen** antagonist if the second affinity is substantially less than the first affinity;

(4) screening for denatured **collagen** antagonists comprising selecting an antagonist for the ability to compete with (I) for binding an epitope in denatured **collagen**; and

(5) a **peptide** comprising a sequence encoding an epitope recognized by (I).

ACTIVITY - Cytostatic.

Systemic administration of monoclonal **antibody HUIV26** inhibited melanoma tumor growth by 80 % compared to controls.

MECHANISM OF ACTION - **Angiogenesis inhibitor**

.

Systemic administration of monoclonal **antibody XL313 inhibited angiogenesis** in the chick CAM model by over 95 % compared to controls.

USE - To **inhibit angiogenesis** in tissue, especially inflamed tissue. To **inhibit** tumor growth or metastasis, especially melanoma, carcinoma, sarcoma, fibrosarcoma, glioma or astrocytoma. (I) may also be used to **inhibit** psoriasis, macular degeneration or restenosis (claimed). (I) can also be used to treat retinal tissue, e.g. diabetic retinopathy or neovascular glaucoma.

Dwg.0/33

L15 ANSWER 9 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:240292 BIOSIS
DOCUMENT NUMBER: PREV200000240292

TITLE: Matrix metalloproteinase inhibitors: Applications in oncology.
AUTHOR(S): Yip, Desmond; Ahmad, Athar; Karapetis, Christos S.; Hawkins, Carolyn A.; Harper, Peter G. (1)
CORPORATE SOURCE: (1) Department of Medical Oncology, Guy's Hospital, St Thomas St, London, SE1 9RT UK
SOURCE: Investigational New Drugs, (1999) Vol. 17, No. 4, pp. 387-399.
ISSN: 0167-6997.
DOCUMENT TYPE: General Review
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Matrix metalloproteinases (MMP) are a group of zinc dependent enzymes which include the interstitial collagenases, stromelysins, gelatinases and membrane-type metalloproteinases. They are involved in the remodelling and turnover of the extracellular matrix **proteins**. They play a role in wound healing and the pathogenesis of arthritis. In malignancies they play a role in tumor invasion, metastasis and **angiogenesis**. A number of synthetic matrix metalloproteinase **inhibitors** (MMPIs) have been developed for clinical use. In preclinical tumor models they have shown promising activity in achieving **inhibition** of MMPs and reducing tumor growth and metastatic spread. Some have also shown additive or synergistic effects with **cytotoxic agents**. Phase I and II studies in human subjects have defined the main side effects of these agents as being musculoskeletal pains or arthralgias. As they are **cytostatic agents** rather than **cytotoxic** in activity conventional measurements of radiological response for assessment are not applicable in trials. Biological activity has been demonstrated in certain cancers by the effects on levels of tumor markers as surrogate markers of tumor response and also by a fibrotic stromal reaction seen in tumor tissue. Newer agents have been developed with selective **inhibition** of certain MMPs in an attempt to reduce the side effects. A number of phase III human clinical trials evaluating MMPs are being carried out at present but only one has been formally reported so far. This study suggested that marimastat had no survival advantage when compared to chemotherapy with gemcitabine in advanced pancreatic carcinoma. Current trials are assessing efficacy of MMPIs in maintenance of remission after other modalities of therapy or in combination with **cytotoxic agents**. MMPs have also been demonstrated to play an important role in the articular cartilage destruction seen in both rheumatoid arthritis and osteoarthritis. The use of MMPIs in both ex vivo and in vivo models have shown promising results and trials are in process to assess their potential role in the control of articular destruction. The true therapeutic role of MMPIs await the results of these randomized studies.

L15 ANSWER 10 OF 13 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 1998301564 MEDLINE
DOCUMENT NUMBER: 98301564 PubMed ID: 9636139
TITLE: Defining the domains of type I **collagen** involved in heparin- binding and endothelial tube formation.
AUTHOR: Sweeney S M; Guy C A; Fields G B; San Antonio J D
CORPORATE SOURCE: Department of Medicine and the Cardeza Foundation for Hematologic Research, Jefferson Medical College of

Thomas Jefferson University, Philadelphia, PA 19107, USA.
CONTRACT NUMBER: AR01929 (NIAMS)
KD44494
R29 HL53590 (NHLBI)
SOURCE: PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1998 Jun 23) 95 (13) 7275-80.
Journal code: 7505876. ISSN: 0027-8424.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199808
ENTRY DATE: Entered STN: 19980817
Last Updated on STN: 20000303
Entered Medline: 19980806

AB Cell surface heparan sulfate proteoglycan (HSPG) interactions with type I **collagen** may be a ubiquitous cell adhesion mechanism. However, the HSPG binding sites on type I **collagen** are unknown. Previously we mapped heparin binding to the vicinity of the type I **collagen** N terminus by electron microscopy. The present study has identified type I **collagen** sequences used for heparin binding and endothelial cell-**collagen** interactions. Using affinity coelectrophoresis, we found heparin to bind as follows: to type I **collagen** with high affinity (Kd approximately 150 nM); **triple-helical peptides** (THPs) including the basic N-terminal sequence alpha1(I)87-92, KGHRGF, with intermediate affinities (Kd approximately 2 microM); and THPs including other collagenous sequences, or single-stranded sequences, negligibly (Kd >> 10 microM). Thus, heparin-type I **collagen** binding likely relies on an N-terminal basic **triple-helical** domain represented once within each monomer, and at multiple sites within fibrils. We next defined the features of type I **collagen** necessary for **angiogenesis** in a system in which type I **collagen** and heparin rapidly induce endothelial tube formation in vitro. When **peptides**, denatured or monomeric type I **collagen**, or type V **collagen** was substituted for type I **collagen**, no tubes formed. However, when **peptides** and type I **collagen** were tested together, only the most heparin-avid THPs **inhibited** tube formation, likely by influencing cell interactions with **collagen**-heparin complexes. Thus, induction of endothelial tube morphogenesis by type I **collagen** may depend upon its **triple-helical** and fibrillar conformations and on the N-terminal heparin-binding site identified here.

L15 ANSWER 11 OF 13 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1999016493 MEDLINE
DOCUMENT NUMBER: 99016493 PubMed ID: 9800111
TITLE: Emerging treatments for epidemic (AIDS-related) Kaposi's sarcoma.
AUTHOR: McGarvey M E; Tulpule A; Cai J; Zheng T; Masood R; Espina B; Arora N; Smith D L; Gill P S
CORPORATE SOURCE: University of Southern California, Los Angeles Department of Medicine and Pathology, Norris Cancer

Hospital and Research Institute 90033, USA.
SOURCE: CURRENT OPINION IN ONCOLOGY, (1998 Sep) 10 (5) 413-21. Ref: 50
Journal code: 9007265. ISSN: 1040-8746.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199812
ENTRY DATE: Entered STN: 19990115
Last Updated on STN: 19990115
Entered Medline: 19981223

AB Kaposi's sarcoma (KS) is an opportunistic tumor that develops with increased frequency (100,000-fold) after HIV infection. KS causes significant morbidity from mucocutaneous involvement and mortality from complications of visceral sites of disease such as the lungs, gastrointestinal tract, and the liver. Progressive unraveling of the KS pathogenesis has lead to the development of novel therapeutic approaches. Newest therapies are first evaluated in patients with limited tumor burden. These include: 1) **inhibitors** of **angiogenesis** such as vascular endothelial growth factor signaling **inhibitor** (SU 5416), and several other **inhibitors** of **angiogenesis** such as the dipeptide IM 862, TNP-470, Col-3, and thalidomide; 2) topical and systemic retinoids; 3) antiviral agents specific for Kaposi's sarcoma herpesvirus and human herpesvirus-8, or HIV; and 4) pregnancy-related factors. Patients with advanced disease such as widespread mucocutaneous disease, lymphedema, and visceral disease are treated most effectively with **cytotoxic agents** . The most active **agents** include liposomal anthracyclines, paclitaxel, vinca alkaloids, and bleomycin. The combination of liposomal anthracyclines and paclitaxel, with and without the most promising biologicals, should now be studied to further reduce the toxicity, and enhance the antitumor effects. Furthermore, identification of risk factors for KS should serve to explore prophylactic therapies.

L15 ANSWER 12 OF 13 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 1998:122567 SCISEARCH
THE GENUINE ARTICLE: YV138
TITLE: Complete primary structure of two variant forms of human type XVIII **collagen** and tissue-specific differences in the expression of the corresponding transcripts
AUTHOR: Saarela J; Ylikarppa R; Rehn M; Purmonen S; Pihlajaniemi T (Reprint)
CORPORATE SOURCE: UNIV OULU, DEPT BIOCHEM MED, KAJAANINTIE 52 A, SF-90220 OULU, FINLAND (Reprint); UNIV OULU, DEPT BIOCHEM MED, SF-90220 OULU, FINLAND; UNIV OULU, BIOCTR, COLLAGEN RES UNIT, SF-90220 OULU, FINLAND
COUNTRY OF AUTHOR: FINLAND
SOURCE: MATRIX BIOLOGY, (JAN 1998) Vol. 16, No. 6, pp. 319-328.
Publisher: GUSTAV FISCHER VERLAG, VILLENGANG 2, D-07745 JENA, GERMANY.
ISSN: 0945-053X.

DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 24
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We report on full-length human type XVIII **collagen** cDNAs that encode 1516- or 1336- residue al(XVIII) chains. The two chains have different signal **peptides** and variant N-terminal non-collagenous NC1 domains of 493 (NC1-493) and 303 (NC1-303) amino acid residues, respectively, but share 301 residues of their NC1 domains, a 688-residue highly interrupted collagenous portion, and a 312-residue C-terminal non-collagenous portion. Al ternative splicing affecting a 43-residue stretch at the junction of tile NC1 domain and the beginning of the collagenous portion was identified. The amino acid sequences' of the human and previously characterized mouse alpha 1(XVIII) chains exhibit an overall identity of 79%. The highest homology between these chains was observed in their last 184 residues, corresponding to the proteolytic fragment endostatin, which is capable of **inhibiting** endothelial cell proliferation, **angiogenesis** and tumor growth (O'Reilly, et al., Cell 88: 277-285,1997).

Northern analysis of several adult and fetal tissues with a probe for the NC1-493 variant revealed marked amounts of the corresponding 6.2 and 5.0 kb mRNAs in liver, while other tissues contained only faint or undetectable signals. Hybridizations with a probe specific for the NC1-303 variant virtually lacked the liver signal but revealed clear 5.6 and 4.5 kb bands in heart, kidney, placenta, prostate, ovaries, skeletal muscle and small intestine, and faint signals in several other tissues. Thus mRNAs for the long variant occur prominently in liver, while those for the short variant appear to be the major ones in the other tissues analyzed.

L15 ANSWER 13 OF 13 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 96185207 EMBASE
DOCUMENT NUMBER: 1996185207
TITLE: Matrix metalloproteinases and tumor invasion: From correlation and causality to the clinic.
AUTHOR: Stetler-Stevenson W.G.; Hewitt R.; Corcoran M.
CORPORATE SOURCE: Division of Clinical Sciences, National Cancer Institute, National Institutes of Health,Bethesda, MD 20892, United States
SOURCE: Seminars in Cancer Biology, (1996) 7/3 (147-154).
ISSN: 1044-579X CODEN: SECBE7
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Tumor cell invasion is now viewed as dysregulated physiologic invasion. Investigators have started to define the molecular events that are involved in this process. We find that there are many functional similarities with molecular events involved in physiologic process such as **angiogenesis** and wound healing. Matrix metalloproteinase activity is a common denominator

in these pathologic conditions and in normal responses. Studies using endogenous metalloproteinase **inhibitors** suggest that targeting matrix metalloproteinase activity may prevent tumor cell dissemination. The development and pre-clinical testing of novel, low molecular weight matrix metalloproteinase **inhibitors** support this concept and suggest that an exciting new era of cancer therapy is on the horizon.

(FILE 'MEDLINE' ENTERED AT 12:35:10 ON 26 MAR 2003)

L16	1429	SEA	FILE=MEDLINE	ABB=ON PLU=ON	"ANGIOGENESIS INHIBITORS "/CT
L17	52387	SEA	FILE=MEDLINE	ABB=ON PLU=ON	COLLAGEN/CT
L18	159	SEA	FILE=MEDLINE	ABB=ON PLU=ON	L16 AND L17
L19	59290	SEA	FILE=MEDLINE	ABB=ON PLU=ON	ANTIBODIES/CT
L20	3	SEA	FILE=MEDLINE	ABB=ON PLU=ON	L18 AND L19

L20 ANSWER 1 OF 3 MEDLINE
AN 2002000069 MEDLINE
TI Microencapsulation of an anti-VE-cadherin antibody secreting 1B5 hybridoma cells.
AU Orive G; Hernandez R M; Gascon A R; Igartua M; Rojas A; Pedraz J L
SO BIOTECHNOLOGY AND BIOENGINEERING, (2001 Dec) 76 (4) 285-94. Journal code: 7502021. ISSN: 0006-3592.
AB Accumulating experimental evidence demonstrates that tumor growth and lethality are dependent on angiogenesis. Based on this concept, there is growing interest in the use of antiangiogenesis agents to inhibit tumor expansion. Compelling data implicate vascular endothelium (VE)-cadherin (an endothelium specific protein) as a key factor in the last step of angiogenesis, where the endothelial cells join one to each other and form microtubules (future blood vessels). We propose a novel approach to the inhibition of angiogenesis by immobilizing VE-cadherin-secreting hybridoma cells in alginate-agarose microcapsules. Hybridoma cells can be protected with biocompatible and semipermeable membranes that permit exit of anti-VE-cadherin monoclonal antibodies but not entry of cellular immune mediators. Stability studies were performed to select the suitable microcapsule for cell immobilization. Alginate and agarose solid beads coated with poly-L-lysine and alginate were chosen according to their stability and diffusional properties. 1B5 hybridoma cells were grown within the microcapsules and secreted anti-VE-cadherin antibodies during the 9 days of culture, reaching a cumulative concentration of 1.7 microg/mL. This antibody concentration inhibited microtubule formation (87%) in the in vitro angiogenesis Matrigel assay. Moreover, the antiangiogenic effect observed was antibody concentration related. These findings open a new alternative for the inhibition or prevention of angiogenesis and demonstrates the feasibility of using microencapsulated cells as a control-drug delivery system.
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L20 ANSWER 2 OF 3 MEDLINE
AN 2001681558 MEDLINE
TI General aspects of anti-angiogenesis and cancer therapy.
AU Zogakis T G; Libutti S K
SO Expert Opin Biol Ther, (2001 Mar) 1 (2) 253-75. Ref: 210 Journal code: 101125414. ISSN: 1471-2598.
AB Angiogenesis is the outgrowth of new vessels from pre-existing ones. Tumour growth and metastasis is dependent on angiogenesis and many

stimulatory and inhibitory factors have been described which play an active role in this process. Inhibition of tumour neovasculature may be one strategy to inhibit tumour growth. Naturally occurring inhibitors of angiogenesis have been discovered and synthetic agents have been designed. Many of these inhibitors are currently being evaluated in clinical trials for the treatment of cancer. This review discusses the mechanism of action of these anti-angiogenics as well as a description of the clinical trials in which they are being evaluated.

L20 ANSWER 3 OF 3 MEDLINE
AN 2001027454 MEDLINE
TI Expression of antisense to integrin subunit beta 3 inhibits microvascular endothelial cell capillary tube formation in fibrin.
AU Dallabrida S M; De Sousa M A; Farrell D H
SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2000 Oct 13) 275 (41) 32281-8. Journal code: 2985121R. ISSN: 0021-9258.
AB alpha(v)beta(3) antagonists are potent angiogenesis inhibitors, and several different classes of inhibitors have been developed, including monoclonal antibodies, synthetic peptides, and small organic molecules. However, each class of inhibitor works by the same principal, by blocking the binding of ligands to alpha(v)beta(3). In an effort to develop an alpha(v)beta(3) inhibitor that down-regulates the actual level of alpha(v)beta(3), we developed an antisense strategy to inhibit alpha(v)beta(3) expression in vitro. beta(3) antisense expressed in endothelial cells specifically down-regulated alpha(v)beta(3) and inhibited capillary tube formation, with the extent of down-regulation correlating with the extent of tube formation inhibition. This inhibition was matrix-specific, since tube formation was not inhibited in Matrigel. These findings support the notion that alpha(v)beta(3) is required for an essential step of angiogenesis in fibrin, namely capillary tube formation. These results suggest that pseudogenetic inhibition of beta(3) integrins using antisense techniques may ultimately provide a therapeutic means to inhibit angiogenesis in vivo.

FILE 'TOXCENTER' ENTERED AT 12:36:28 ON 26 MAR 2003
L21 2 S L9
L22 2 S L10
L23 4 S L21 OR L22

L23 ANSWER 1 OF 4 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:181606 TOXCENTER
DOCUMENT NUMBER: 21426955 PubMed ID: 11535623
TITLE: Proteolytic exposure of a cryptic site within **collagen** type IV is required for angiogenesis and tumor growth in vivo
COMMENT: Erratum in: J Cell Biol 2001 Nov 26;155(5):859
Erratum in: Yuen SM [corrected to Moon YS]
AUTHOR(S): Xu J; Rodriguez D; Petitclerc E; Kim J J; Hangai M; Moon Y S; Davis G E; Brooks P C; Yuen S M
CORPORATE SOURCE: Department of Radiation Oncology, Kaplan Cancer Center, New York University School of Medicine, New York, NY 10016, USA
CONTRACT NUMBER: CA086140 (NCI)
CA74132 (NCI)
HL59971 (NHLBI)

SOURCE: JOURNAL OF CELL BIOLOGY, (2001 Sep 3) 154 (5) 1069-79.
Journal Code: 0375356. ISSN: 0021-9525.
COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: MEDLINE
OTHER SOURCE: MEDLINE 2001493142
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20020129

AB Evidence is provided that proteolytic cleavage of **collagen** type IV results in the exposure of a functionally important cryptic site hidden within its **triple helical** structure. Exposure of this cryptic site was associated with angiogenic, but not quiescent, blood vessels and was required for angiogenesis in vivo. Exposure of the **HUIV26** epitope was associated with a loss of alphalbeta1 integrin binding and the gain of alphavbeta3 binding. A monoclonal **antibody** (**HUIV26**) directed to this site disrupts integrin-dependent endothelial cell interactions and potently **inhibits angiogenesis** and tumor growth. Together, these studies suggest a novel mechanism by which proteolysis contributes to angiogenesis by exposing hidden regulatory elements within matrix-immobilized **collagen** type IV.

L23 ANSWER 2 OF 4 TOXCENTER COPYRIGHT 2003 ACS

ACCESSION NUMBER: 2000:168177 TOXCENTER
COPYRIGHT: Copyright 2003 ACS
DOCUMENT NUMBER: CA133080995695
TITLE: Method and composition for **angiogenesis inhibition** and detection using antagonists binding to proteolyzed or denatured **collagen**
AUTHOR(S): Brooks, Peter; Petitclerc, Eric; Xu, Jingsong
CORPORATE SOURCE: ASSIGNEE: University of Southern California
PATENT INFORMATION: WO 2000040597 A1 13 Jul 2000
SOURCE: (2000) PCT Int. Appl., 92 pp.
CODEN: PIXXD2.
COUNTRY: UNITED STATES
DOCUMENT TYPE: Patent
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 2000:475678
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20020326

AB The invention describes methods for **inhibiting angiogenesis** in a tissue by administering an antagonist that specifically binds to a proteolyzed or denatured **collagen** but not to native **triple helical** forms of the **collagen**. Antagonists of the invention can target e.g. denatured **collagens** type I, type II, type III, type IV, type V, and combinations thereof. Methods using such antagonists for therapeutic treatment of tumor growth, tumor metastasis or of restenosis also are described, as are methods to use such antagonists as diagnostic markers of angiogenesis in normal or diseased tissues both in vivo and ex vivo. Antagonists include monoclonal **antibodies** referred to as HUI77, **HUIV26**, and **XL313**.

L23 ANSWER 3 OF 4 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:147239 TOXCENTER
COPYRIGHT: Copyright 2003 ACS
DOCUMENT NUMBER: CA132253306322
TITLE: **Protein** and cDNA sequences of endostatin, and therapeutic anti-angiogenic compositions derived therefrom
AUTHOR(S): O'Reilly, Michael S.; Folkman, M. Judah
CORPORATE SOURCE: ASSIGNEE: The Children's Medical Center Corporation
PATENT INFORMATION: WO 2000026368 A2 11 May 2000
SOURCE: (2000) PCT Int. Appl., 68 pp.
CODEN: PIXXD2.
COUNTRY: UNITED STATES
DOCUMENT TYPE: Patent
FILE SEGMENT: CAPLUS
OTHER SOURCE: CAPLUS 2000:314832
LANGUAGE: English
ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20020416

AB The invention provides **protein** and cDNA sequences of a novel **inhibitor** of **angiogenesis** (endostatin) which is useful for treating **angiogenesis**-related cancer and/or related disorders. Endostatin has a mol. wt. of approx. 10 to 20 kDa, is capable of inhibiting endothelial cell proliferation in cultured endothelial cells, and can be further characterized by its N-terminal amino acid sequence which has identity to a C-terminal fragment of the NC1 domain of **collagen** XVIII. Endostatin compns. capable of **inhibiting** endothelial cell proliferation, **inhibiting angiogenesis** and causing tumor regression are described. The invention further relates to diagnostic assays and kits for endostatin measurement, to histochem. kits for localization of endostatin, to mol. probes to monitor endostatin biosynthesis, to **antibodies** that are specific for the endostatin, to the development of **peptide** agonists and antagonists to the endostatin receptor, and to **cytotoxic agents** linked to endostatin **peptides**.

L23 ANSWER 4 OF 4 TOXCENTER COPYRIGHT 2003 ACS
ACCESSION NUMBER: 1999:5431 TOXCENTER
DOCUMENT NUMBER: 99016493 PubMed ID: 9800111
TITLE: Emerging treatments for epidemic (AIDS-related) Kaposi's sarcoma
AUTHOR(S): McGarvey M E; Tulpule A; Cai J; Zheng T; Masood R; Espina B; Arora N; Smith D L; Gill P S
CORPORATE SOURCE: University of Southern California, Los Angeles Department of Medicine and Pathology, Norris Cancer Hospital and Research Institute 90033, USA
SOURCE: CURRENT OPINION IN ONCOLOGY, (1998 Sep) 10 (5) 413-21. Ref: 50.
Journal Code: 9007265. ISSN: 1040-8746.
COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
FILE SEGMENT: MEDLINE
OTHER SOURCE: MEDLINE 1999016493
LANGUAGE: English

ENTRY DATE: Entered STN: 20011116
Last Updated on STN: 20011116

AB Kaposi's sarcoma (KS) is an opportunistic tumor that develops with increased frequency (100,000-fold) after HIV infection. KS causes significant morbidity from mucocutaneous involvement and mortality from complications of visceral sites of disease such as the lungs, gastrointestinal tract, and the liver. Progressive unraveling of the KS pathogenesis has lead to the development of novel therapeutic approaches. Newest therapies are first evaluated in patients with limited tumor burden. These include: 1) **inhibitors** of **angiogenesis** such as vascular endothelial growth factor signaling **inhibitor** (SU 5416), and several other **inhibitors** of **angiogenesis** such as the dipeptide IM 862, TNP-470, Col-3, and thalidomide; 2) topical and systemic retinoids; 3) antiviral agents specific for Kaposi's sarcoma herpesvirus and human herpesvirus-8, or HIV; and 4) pregnancy-related factors. Patients with advanced disease such as widespread mucocutaneous disease, lymphedema, and visceral disease are treated most effectively with **cytotoxic agents** . The most active agents include liposomal anthracyclines, paclitaxel, vinca alkaloids, and bleomycin. The combination of liposomal anthracyclines and paclitaxel, with and without the most promising biologicals, should now be studied to further reduce the toxicity, and enhance the antitumor effects. Furthermore, identification of risk factors for KS should serve to explore prophylactic therapies.

FILE 'HCAPLUS' ENTERED AT 12:37:20 ON 26 MAR 2003
L24 4 S L8 AND (TRIPLE OR THREE)(S)(HELIX OR HELICAL?)
L25 0 S L24 NOT L11

FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 12:38:03 ON 26 MAR 2003
L26 19 S L24
L27 0 S L26 NOT L14

FILE 'TOXCENTER' ENTERED AT 12:39:45 ON 26 MAR 2003
L28 2 S L24
L29 0 S L28 NOT L23

(FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT, TOXCENTER' ENTERED AT 12:40:23 ON 26 MAR 2003)
L30 4063 S BROOKS P?/AU
L31 132 S PETITCLERC E?/AU
L32 26243 S XU J?/AU
L33 22 S L30 AND L31 AND L32
L34 67 S L30 AND (L31 OR L32)
L35 22 S L31 AND L32

L37 31 S (L34 OR L30 OR L31 OR L32) AND L8
L38 39 S L33 OR L35 OR L37
L39 13 DUP REM L38 (26 DUPLICATES REMOVED)

- Author(s)

L39 ANSWER 1 OF 13 HCAPLUS COPYRIGHT 2003 ACS DUPLICATE 1
ACCESSION NUMBER: 2002:839038 HCAPLUS
DOCUMENT NUMBER: 138:105028
TITLE: Matrix metalloproteinase-9-dependent exposure of

a cryptic migratory control site in **collagen** is required before retinal angiogenesis

AUTHOR(S): Hangai, Masanori; Kitaya, Norihiko; **Xu, Jingsong**; Chan, Candy K.; Kim, Jenny J.; Werb, Zena; Ryan, Stephen J.; **Brooks, Peter C.**

CORPORATE SOURCE: Department of Ophthalmology, Kobe City General Hospital, Kobe, Japan

SOURCE: American Journal of Pathology (2002), 161(4), 1429-1437
CODEN: AJPAA4; ISSN: 0002-9440
PUBLISHER: American Society for Investigative Pathology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Retinal neovascularization is a leading cause of human blindness. However, little is known concerning the mol. mechanisms controlling retinal neovascularization in vivo. Here we provide evidence that exposure of a **collagen** type N cryptic epitope detected by monoclonal **antibody** (**mAb**) **HUIV26**, delineates sites of vascular bud formation and represents one of the earliest structural remodeling events required before vessel out-growth. Exposure of these cryptic sites was inhibited in matrix metalloproteinase (MMP)-9-deficient but not MMP-2-deficient mice implicating MMP-9 in their exposure. Retinal endothelial cell interactions with the **HUIV26** epitopes induced endothelial cell migration, which was blocked by **mAb HUIV26**. Importantly, s.c. administration of **mAb HUIV26** potently **inhibited** retinal **angiogenesis** in vivo. Taken together, these findings suggest a novel mechanism in which MMP-9 facilitates exposure of **HUIV26** cryptic sites, thereby promoting retinal endothelial cell migration and neovascularization in vivo.

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 2 OF 13 HCAPLUS COPYRIGHT 2003 ACS DUPLICATE 2

ACCESSION NUMBER: 2002:839607 HCAPLUS

TITLE: Ionizing radiation modulates the exposure of the **HUIV26** cryptic epitope within **collagen** type IV during angiogenesis

AUTHOR(S): **Brooks, Peter C.**; Roth, Jennifer M.; Lymberis, Stella C.; DeWyngaert, Keith; Broek, Daniel; Formenti, Silvia C.

CORPORATE SOURCE: Department of Radiation Oncology, New York University School of Medicine, New York, NY, USA

SOURCE: International Journal of Radiation Oncology, Biology, Physics (2002), 54(4), 1194-1201
CODEN: IOBPD3; ISSN: 0360-3016
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Purpose: The majority of the research on the biol. effects of ionizing radiation has focused on the impact of radiation on cells in terms of gene expression, DNA damage, and cytotoxicity. In comparison, little information is available concerning the direct effects of radiation on the extracellular microenvironment,

specifically the extracellular matrix and its main component, **collagen**. We have developed a series of monoclonal **antibodies** that bind to cryptic epitopes of **collagen** Type IV that are differentially exposed during matrix remodeling and are key mediators of angiogenesis. We have hypothesized that ionizing radiation might affect the process of angiogenesis through a direct effect on the extracellular matrix and specifically on **collagen** Type IV. Methods and Materials: Angiogenesis was induced in a chick chorioallantoic membrane (CAM) model; 24 h later, a single-dose treatment with ionizing radiation (0.5, 5, and 20 cGy) was administered. **Angiogenesis** was assessed, and the exposure of two cryptic regulatory epitopes within **collagen** Type IV (HUI77 and **HUIV26**) was studied in vitro by solid-phase ELISA and in vivo by immunofluorescence staining. Results: A dose-dependent redn. of **angiogenesis** with max. **inhibition** (85%-90%) occurring at 20 cGy was demonstrated in the CAM model. Exposure of the cryptic **HUIV26** site, an **angiogenesis** control element, was **inhibited** both in vitro and in vivo by the same radiation dose, whereas little if any change was obsd. for the HUI77 cryptic epitope. Conclusions: A dose-dependent alteration of the functional exposure of the **HUIV26** cryptic epitope is induced by radiation in vitro and in the CAM model in vivo. This radiation-induced change in **protein** structure and function may contribute to the inhibitory effects of ionizing radiation on new blood vessel growth and warrants further studies in other models.

REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 3 OF 13 HCAPLUS COPYRIGHT 2003 ACS DUPLICATE 3

ACCESSION NUMBER: 2001:660699 HCAPLUS
DOCUMENT NUMBER: 135:342351
TITLE: Proteolytic exposure of a cryptic site within **collagen** type IV is required for angiogenesis and tumor growth in vivo
AUTHOR(S): **Xu, Jingsong**; Rodriguez, Dorothy; **Petitclerc, Eric**; Kim, Jenny J.; Hangai, Masanori; Yuen, S. Moon; Davis, George E.; **Brooks, Peter C.**
CORPORATE SOURCE: Departments of Radiation Oncology and Cell Biology, Kaplan Cancer Center, New York University School of Medicine, New York, NY, 10016, USA
SOURCE: Journal of Cell Biology (2001), 154(5), 1069-1079
CODEN: JCLBA3; ISSN: 0021-9525
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Evidence is provided that proteolytic cleavage of **collagen** type IV results in the exposure of a functionally important cryptic site hidden within its triple helical structure. Exposure of this cryptic site was assocd. with angiogenic, but not quiescent, blood vessels and was required for angiogenesis in vivo. Exposure of the **HUIV26** epitope was assocd. with a loss of .alpha.1.beta.1 integrin binding and the gain of .alpha.v.beta.3 binding. A monoclonal **antibody** (**HUIV26**) directed to this

site disrupts integrin-dependent endothelial cell interactions and potently **inhibits angiogenesis** and tumor growth. Together, these studies suggest a novel mechanism by which proteolysis contributes to angiogenesis by exposing hidden regulatory elements within matrix-immobilized **collagen** type IV.

REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 4 OF 13 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2001:879702 HCAPLUS
TITLE: Vol. 154, No. 5, September 3, 2001. Pages 1069-1079
AUTHOR(S): **Xu, Jingsong**; Rodriguez, Dorothy; **Petitclerc, Eric**; Kim, Jenny J.; Hangai, Masanori; Moon, Yeon Sung; Davis, George E.; **Brooks, Peter C.**
SOURCE: J. Cell Biol. (2001), 155(5), 859 CODEN: JCLBA3; ISSN: 0021-9525
PUBLISHER: Rockefeller University Press
DOCUMENT TYPE: Journal; Errata
LANGUAGE: English
AB Unavailable

L39 ANSWER 5 OF 13 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 2002130938 EMBASE
TITLE: Erratum: S. Moon Yuen (The Journal of Cell Biolgy (September 3, 2001) 154:5 (1069-1079)).
AUTHOR: **Xu J.**; Rodriguez D.; **Petitclerc E.**; Kim J.J.; Hangai M.; Moon Y.S.; Davis G.E.; **Brooks P.C.**
SOURCE: Journal of Cell Biology, (26 Nov 2001) 155/5 (859). ISSN: 0021-9525 CODEN: JCLBA3
COUNTRY: United States
DOCUMENT TYPE: Journal; Errata
FILE SEGMENT: 029 Clinical Biochemistry
LANGUAGE: English

L39 ANSWER 6 OF 13 SCISEARCH COPYRIGHT 2003 ISI (R)
ACCESSION NUMBER: 2001:962272 SCISEARCH
THE GENUINE ARTICLE: 497MQ
TITLE: Proteolytic exposure of a cryptic site within collagen type IV is required for angiogenesis and tumor growth in vivo (vol 154, pg 1069, 2001)
AUTHOR: **Xu J S (Reprint)**; Rodriguez D; **Petitclerc E**; Kim J J; Hangai M; Moon Y S; Davis G E; **Brooks P C**
SOURCE: JOURNAL OF CELL BIOLOGY, (26 NOV 2001) Vol. 155, No. 5, pp. 859-859. Publisher: ROCKEFELLER UNIV PRESS, 1114 FIRST AVE, 4TH FL, NEW YORK, NY 10021 USA. ISSN: 0021-9525.
DOCUMENT TYPE: Errata; Journal
LANGUAGE: English
REFERENCE COUNT: 1

L39 ANSWER 7 OF 13 HCAPLUS COPYRIGHT 2003 ACS DUPLICATE 4

ACCESSION NUMBER: 2000:475678 HCAPLUS
DOCUMENT NUMBER: 133:99569
TITLE: Method and composition for **angiogenesis inhibition** and detection using antagonists binding to proteolyzed or denatured **collagen**
INVENTOR(S): **Brooks, Peter; Petitclerc, Eric; Xu, Jingsong**
PATENT ASSIGNEE(S): University of Southern California, USA
SOURCE: PCT Int. Appl., 92 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000040597	A1	20000713	WO 2000-US383	20000106
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2358517	AA	20000713	CA 2000-2358517	20000106
EP 1149111	A1	20011031	EP 2000-904246	20000106
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002539076	T2	20021119	JP 2000-592305	20000106

PRIORITY APPLN. INFO.:
US 1999-114877P P 19990106
US 1999-114878P P 19990106
US 1999-143534P P 19990713
US 1999-152496P P 19990902
WO 2000-US383 W 20000106

AB The invention describes methods for **inhibiting angiogenesis** in a tissue by administering an antagonist that specifically binds to a proteolyzed or denatured **collagen** but not to native triple helical forms of the **collagen**. Antagonists of the invention can target e.g. denatured **collagens** type I, type II, type III, type IV, type V, and combinations thereof. Methods using such antagonists for therapeutic treatment of tumor growth, tumor metastasis or of restenosis also are described, as are methods to use such antagonists as diagnostic markers of angiogenesis in normal or diseased tissues both in vivo and ex vivo. Antagonists include monoclonal **antibodies** referred to as HUI77, **HUIV26**, and **XL313**.

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 8 OF 13 HCAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:725489 HCAPLUS
DOCUMENT NUMBER: 133:276344

TITLE: The use of domains of type IV **collagen** to **inhibit angiogenesis** and tumour growth
INVENTOR(S): **Brooks, Peter**; Hudson, Billy
PATENT ASSIGNEE(S): Biostratum, Inc., USA
SOURCE: PCT Int. Appl., 78 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000059532	A1	20001012	WO 2000-US8678	20000331

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-127391P P 19990401

AB The instant invention provides methods and kits for **inhibiting angiogenesis**, tumor growth and metastasis, and endothelial cell interactions with the extracellular matrix, involving contacting the tumor, animal tissue, or endothelial cells with an amt. effective to **inhibit angiogenesis**, tumor growth and metastasis, or endothelial cell interactions with the extracellular matrix of an antagonist of specific integrin receptors.

REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 9 OF 13 HCAPLUS COPYRIGHT 2003 ACS DUPLICATE 5
ACCESSION NUMBER: 2000:208665 HCAPLUS
DOCUMENT NUMBER: 133:26565
TITLE: New functions for non-collagenous domains of human **collagen** type IV. Novel integrin ligands **inhibiting angiogenesis** and tumor growth in vivo
AUTHOR(S): **Petitclerc, Eric**; Boutaud, Ariel; Prestayko, Archie; **Xu, Jingsong**; Sado, Yoshikazu; Ninomiya, Yoshifumi; Sarras, Michael P., Jr.; Hudson, Billy G.; **Brooks, Peter C.**
CORPORATE SOURCE: Department of Biochemistry and Molecular Biology, University of Southern California School of Medicine, Los Angeles, CA, 90033, USA
SOURCE: Journal of Biological Chemistry (2000), 275(11), 8051-8061
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal

LANGUAGE: English

AB **Collagen** type IV is a major component of the basal lamina of blood vessels. Six genetically distinct **collagen** type IV chains have been identified and are distributed in a tissue-specific manner. Here we define a novel function for sol. non-collagenous (NC1) domains of the .alpha.2(IV), .alpha.3(IV), and .alpha.6(IV) chains of human **collagen** type IV in the regulation of angiogenesis and tumor growth. These NC1 domains were shown to regulate endothelial cell adhesion and migration by distinct .alpha.v and .beta.1 integrin-dependent mechanisms. Systemic administration of recombinant .alpha.2(IV), .alpha.3(IV), and .alpha.6(IV) NC1 domains potently **inhibit angiogenesis** and tumor growth, whereas .alpha.1(IV), .alpha.4(IV), and .alpha.5(IV) showed little if any effect. These findings suggest that specific NC1 domains of **collagen** type IV may represent an important new class of **angiogenesis inhibitors.**

REFERENCE COUNT: 60 THERE ARE 60 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L39 ANSWER 10 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:251197 BIOSIS
DOCUMENT NUMBER: PREV200000251197
TITLE: Angiogenic cryptic site of proteolyzed subendothelial type IV **collagen** as a novel target to treat retinal neovascularization.
AUTHOR(S): Hangai, M. (1); Kitaya, N. (1); Chan, C. K. (1); **Xu, J.**; Kim, J. J.; Ryan, S. J. (1); **Brooks, P. C.**
CORPORATE SOURCE: (1) Department of Ophthalmology, Doheny Eye Institute, Keck School of Medicine at the University of Southern California, Los Angeles, CA USA
SOURCE: IOVS, (March 15, 2000) Vol. 41, No. 4, pp. S641. Meeting Info.: Annual Meeting of the Association in Vision and Opthalmology. Fort Lauderlade, Florida, USA April 30-May 05, 2000 Association for Research in Vision and Ophthalmology
.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L39 ANSWER 11 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:225039 BIOSIS
DOCUMENT NUMBER: PREV200000225039
TITLE: Proteolytic exposure of a cryptic site within collagen-IV regulates angiogenesis and tumor growth in vivo.
AUTHOR(S): **Xu, Jingsong (1)**; Rodriguez, D. (1); Kim, J. J. (1); **Petitclerc, E. (1)**; Hangai, M. (1); Davis, G. E. (1); **Brooks, P. C. (1)**
CORPORATE SOURCE: (1) Univ of Southern CA, Los Angeles, CA USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 487.
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco,

California, USA April 01-05, 2000
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L39 ANSWER 12 OF 13 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 2000:215726 BIOSIS
DOCUMENT NUMBER: PREV200000215726
TITLE: New functions for NC1 domains of human collagen-IV: Novel integrin ligands inhibiting angiogenesis and tumor growth in vivo.
AUTHOR(S): **Petitclerc, Eric (1)**; Boutaud, A. (1); Prestayko, A. (1); **Xu, J. (1)**; Sado, Y. (1); Ninomiya, Y. (1); Hudson, B. G. (1); **Brooks, P. C. (1)**
CORPORATE SOURCE: (1) U Southern CA, Los Angeles, CA USA
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (March, 2000) No. 41, pp. 487.
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco, California, USA April 01-05, 2000
ISSN: 0197-016X.
DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L39 ANSWER 13 OF 13 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 1998135765 MEDLINE
DOCUMENT NUMBER: 98135765 PubMed ID: 9476898
TITLE: Disruption of angiogenesis by PEX, a noncatalytic metalloproteinase fragment with integrin binding activity.
AUTHOR: **Brooks P C**; Silletti S; von Schalscha T L; Friedlander M; Cheresh D A
CORPORATE SOURCE: Department of Immunology, The Scripps Research Institute, La Jolla, California 92037, USA.
CONTRACT NUMBER: CA45726 (NCI)
CA50286 (NCI)
HL54444 (NHLBI)
+
SOURCE: CELL, (1998 Feb 6) 92 (3) 391-400.
Journal code: 0413066. ISSN: 0092-8674.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199803
ENTRY DATE: Entered STN: 19980312
Last Updated on STN: 20000303
Entered Medline: 19980304

AB **Angiogenesis** depends on both cell adhesion and proteolytic mechanisms. In fact, matrix metalloproteinase 2 (MMP-2) and integrin alphavbeta3 are functionally associated on the surface of angiogenic blood vessels. A fragment of MMP-2, which comprises the C-terminal hemopexin-like domain, termed PEX, prevents this enzyme binding to alphavbeta3 and blocks cell surface collagenolytic activity. PEX

blocks MMP-2 activity on the chick chorioallantoic membrane where it disrupts **angiogenesis** and tumor growth. Importantly, a naturally occurring form of PEX can be detected in vivo in conjunction with alphavbeta3 expression in tumors and during developmental retinal neovascularization. Levels of PEX in these vascularized tissues suggest that it interacts with endothelial cell alphavbeta3 where it serves as a natural **inhibitor** of MMP-2 activity, thereby regulating the invasive behavior of new blood vessels.

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